[\textsuperscript{123}I]FP-CIT single photon emission computed tomography (DaTSCAN) in the differential diagnosis between dementia with Lewy bodies (DLB) and non-DLB dementia in cases of unclear dementia

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The review will be guided by the following protocol describing research questions, review methods, and plan for data extraction and synthesis.
Introduction

Disturbances of dopaminergic functioning are associated with numerous neurological disorders, whose diagnosis may be challenging, particularly in the early stages.

A diagnosis of dementia with Lewy bodies (DLB) is based on several core clinical features in addition to dementia: cognitive fluctuations with marked variation of attention and alertness, recurrent well-formed, detailed visual hallucinations, and spontaneous (i.e. not drug-induced) parkinsonism [McKeith, 2005]. Other clinical manifestations of DLB may suggest or support the diagnosis [McKeith, 2005].

Frequently, delineating DLB from other dementia syndromes may represent a diagnostic challenge, especially during the first stages of disease. Hence, a reliable test to differentiate DLB from non-DLB dementia would be of utmost importance for an accurate prognosis and management. For instance, about 30-50% of patients with DLB experience severe adverse effects after administration of neuroleptics (such as haloperidol) [McKeith, 1992; Ballard, 1998], with an increased short-term mortality [Aarsland, 2005]. Conversely, these patients may benefit from cholinesterase inhibitor therapy [McKeith, 2000; Ukai, 2014; Wang, 2015].

The functional integrity of dopaminergic nigrostriatal pathway can be studied with single photon emission computed tomography (SPECT) imaging by using ligands of pre-synaptic dopamine transporter (DAT) such as Iodine-123-beta-CIT, Iodine-123-Ioflupane (FP-CIT), Iodine-123-IPT and 99mCT-TRODAT-1. A reduction of SPECT ligand binding to DAT correlates with the loss of presynaptic dopamine. The rationale supporting the use of $[^{123}\text{I}]$FP-CIT SPECT (DaTSCAN) as a supportive tool in the diagnosis of DLB is represented by the pathological peculiarities of DLB, characterized by abnormal inclusion bodies (Lewy bodies) in limbic, neocortical and brainstem areas with concomitant nigrostriatal degeneration and loss of pre-synaptic dopamine transporters in the striatum [McKeith, 2004; Weisman, 2007]. For these reasons, low dopamine transporter uptake in basal ganglia on DaTSCAN has been listed as a feature suggestive of DLB in the international consensus criteria for the diagnosis [McKeith, 2007].

Aim of this study is to systematically review the utility of dopamine system imaging using $[^{123}\text{I}]$FP-CIT SPECT in the differential diagnosis between DLB and non-DLB in cases of unclear dementia. Our choice of focusing only on the use of $[^{123}\text{I}]$FP-CIT SPECT was justified in order to reduce methodological heterogeneity across studies and because this technique is more widely available for routine clinical use than PET or SPECT using other ligands.

Methods
Our aim will be to critically and systematically evaluate the literature to evaluate the diagnostic accuracy of $[^{123}\text{I}]$FP-CIT SPECT in the differential diagnosis between DLB and non-DLB dementia in cases of unclear dementia, determining the sensitivity, specificity, positive and negative likelihood ratio (pLR, nLR), and diagnostic odds ratio of this dopamine system imaging.

We will include prospective and retrospective studies reporting data on $[^{123}\text{I}]$FP-CIT SPECT performed in patient with unclear dementia who underwent $[^{123}\text{I}]$FP-CIT SPECT for further diagnostic assessment.

We will did not consider patients with a clinically defined diagnosis of DLB or non-DLB.

Search methods for identification of studies

Electronic searches
We will search the following databases:
- MEDLINE (accessed by Pubmed);
- the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library);
- ClinicalTrials.gov (available at: https://clinicaltrials.gov/ct2/home).

We present the proposed search strategy for MEDLINE, CENTRAL and ClinicalTrials.gov in Appendix.

Searching other resources
We will review the reference lists of articles retrieved by the electronic searches to check for other relevant reports not indexed in the electronic database. No language restrictions will be applied.

Data collection and analysis
Selection of studies
Two review authors (FB and GT) will independently screen all the titles and abstracts of publications identified by the searches to assess their eligibility. We will exclude publications that do not meet the criteria at this stage. Following screening, we will assess the full-text of potentially-eligible citations for inclusion. The review authors will reach consensus on the selection of trials and the final list of studies. We will discuss any disagreements and resolve them where possible. If we cannot reach consensus, we will consult a third member of the team (MT).
Inclusion criteria

We will include all cross-sectional studies of patients in which $[^{123}\text{I}]$FP-CIT SPECT was tested as a means to differentiate between dementia syndromes, reporting data on SPECT results in patients with DLB and non-DLB dementia. We will exclusively focus on patients with unclear dementia, evaluating the role of $[^{123}\text{I}]$FP-CIT SPECT in differentiating between DLB and non-DLB in cases of unclear dementia. No age, race or gender restrictions will be applied.

Exclusion criteria

The following exclusion criteria will be used:
1) studies not reporting data on SPECT in patients in whom a diagnosis of DLB or non-DLB was eventually made;
2) studies not reporting information to allow the construction of the diagnostic 2 by 2 table with its four cells: true positives, false negatives, true negatives and false positives of both patients with DLB and with non-DLB;
3) studies using SPECT with ligands other than $[^{123}\text{I}]$FP-CIT.

Data extraction

Two review authors (FB and GT) will independently extract data from the published reports where possible. We will use data extraction forms and resolve any disagreements by mutual agreement. We will record the rawest form of the data, when possible. In case of missing or incomplete data, we will contact the principal investigators of included trials and request additional information.

Following data will be extracted:
- author(s);
- year of publication;
- inclusion criteria;
- number of patients;
- age;
- gender;
- disease duration (months/years);
- reference diagnostic standard chosen;
- minimal duration of follow-up after SPECT (months);
- part of the striatum evaluated;
- cut-off point adopted to define SPECT abnormality;
- methods used to judge SPECT results (visual, quantitative);
- independent, blind comparison with clinical diagnosis.

A standardized data extraction form will be used and data on accuracy measure will be reported in a diagnostic 2 by 2 table to calculate sensitivity, specificity, and LRs.

**Methodological quality evaluation**

The methodological quality of each selected paper will be assessed independently by two reviewers (FB and GT).

The quality of the studies provisionally selected for inclusion in the review will be evaluated using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool [Whiting et al., 2003].

Furthermore, we will evaluate whether studies explicitly reported a well-defined cut-off point to define SPECT abnormality.

**Data synthesis**

Provided we think it clinically appropriate, and no important clinical and methodological heterogeneity is found, we plan to synthesize the study results in a meta-analysis.

Sensitivity, specificity and the odds ratio will be calculated for each study separately, and the pooled diagnostic odds ratios (ORs) for all studies together. Considering the presence of methodological heterogeneity and threshold effect, due to differences in patients, SPECT machinery, radiotracers etc., we will use diagnostic ORs [Egger et al., 2005]. The diagnostic ORs express how much greater the odds of having the disease are for the people with a positive test result than for the people with a negative test result. It is a single measure of diagnostic test performance that combines both LRs.

The potential problems associated with sensitivities and specificities of 100% (i.e. studies with zeroes in one or more cells of the diagnostic 2 by 2 table) will be solved by adding 0.5 to all cells of the diagnostic 2 by 2 table [Cox, 1970; McGee, 2007].

Trials with a sensitivity of 100% and a specificity of 0% will not be excluded, however the pooled diagnostic ORs will also calculated without such studies (sensitivity analysis).

Accuracy measures for each study, pooled accuracy measures and diagnostic ORs will be obtained by performing a meta-analysis using Meta-DiSc software 1.4 (available online at: ftp://ftp.hrc.es/pub/programas/metadisc/Metadisc_update.htm) [Zamora et al., 2006a].

Sensitivity, specificity, pLR and nLR with 95% CIs will be determined for each included study and for the summary estimate of pooled analysis using equations reported in Appendix.
Sensitivity measures the proportion of positives that are correctly identified, whereas specificity measures the proportion of negatives that are correctly identified. The LR of a physical sign is defined as the proportion of patients with disease who have a certain finding divided by the proportion of subjects without disease who also have the same finding [McGee, 2007]. A pLR refers to the presence of the physical sign, whereas a nLR refers to the absence of that physical sign. The interpretation of LRs is straightforward: (1) values greater than 1 increase the probability of disease, and the greater the LR, the more compelling the argument for disease; (2) values between 0 and 1 decrease the probability of disease, and the closer the LR is to zero, the more the finding argues against the diagnosis of disease; (3) values equal zero have no diagnostic values, as they do not change pre-test probability [McGee, 2007]. A pLR describes therefore how probability changes when the finding is present, whereas nLR describes how probability changes when the finding is absent.

Diagnostic OR of each study will be combined to obtain a summary estimate of value (and the corresponding 95% confidence intervals, CIs) using a random-effect model. Random-effects model, which considers both within-study and between-study variance to calculate a pooled ORs, will be used to summarize the ORs from the included studies. This model is considered more conservative than a fixed-effect, since it takes into account the variability between studies, thus leading to wider CIs [DerSimonian and Laird, 1986].

**Assessment of heterogeneity**

Visual inspection of the forest plots will be used to investigate the possibility of statistical heterogeneity. We will evaluate homogeneity among trial results using a standard Chi2 test and the hypothesis of homogeneity will be rejected if the P value is less than 0.10.

Assessment of statistical heterogeneity will be supplemented using the I2 statistic which provides an estimate of the percentage of variability due to heterogeneity rather than a sampling error [Higgins et al., 2003].

**Subgroup analysis**

If sufficient data are available, we plan to perform subgroup analyses according to different types of non-DLB dementia syndromes.

**Sensitivity analysis**
The diagnostic ORs in our study may be affected by differences in the individual cut-off points, hence introducing relevant methodological heterogeneity. We therefore will search for the presence of an (implicit) cut-off point effect between studies by calculating a Spearman correlation coefficient between sensitivity and specificity of all included studies. In case of strong negative correlation (i.e. $\rho<0.6$), indicative of strong cut-off effect [Moses et al., 1993], we plan to perform a sensitivity analysis adopting one common cut-off point for all studies. In this sensitivity analysis we plan to include only those studies adopting a cut-off point of 2 standard deviations (SD) below the binding-rate of healthy controls as a definition for abnormal SPECT. We chose this approach to take into consideration the presence of a significant cut-off point effect in the included studies [Vlaar et al., 2007]. We will repeat pooled analyses excluding one study at a time to ensure that the results are not skewed by a single (or a few) outlier. A further sensitivity analysis will be conducted excluding trials with a sensitivity of 100% and a specificity of 100% [Vlaar et al., 2007].

References


olmes C. Neuroleptic sensitivity in dementia with Lewy bodies and Alzheimer's disease.


APPENDIX

Search strategies
MEDLINE:

CENTRAL:
("lewy body disease" OR “lewy body dementia” OR “dementia with Lewy bodies”) AND (SPECT OR DaTSCAN)

ClinicalTrials.gov:
("lewy body disease" OR “lewy body dementia”) AND (SPECT OR DaTSCAN)

Equations used to calculate accuracy measures of SPECT

<table>
<thead>
<tr>
<th>Target disease (LBD)</th>
<th>Absence of target disease (non-LBD dementia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal SPECT</td>
<td>a</td>
</tr>
<tr>
<td>Normal SPECT</td>
<td>c</td>
</tr>
</tbody>
</table>

c1 = a + cnc2 = b + dz = 1.959964

**Sensitivity**

Sensitivity = a/nc1

Lower limit = ((2 × a) + z² − z√((4 × a × c/nc1) + z^2))/((2 × nc1) + (2 × z^2))

Upper limit = ((2 × a) + z² + z√((4 × a × c/nc1) + z^2))/((2 × nc1) + (2 × z^2))

**Specificity**

Specificity = d/nc2

Lower limit = ((2 × d) + z² − z√((4 × d × b/nc2) + z^2))/((2 × nc2) + (2 × z^2))

Upper limit = ((2 × d) + z² + z√((4 × d × b/nc2) + z^2))/((2 × nc2) + (2 × z^2))

**Positive likelihood ratio**

*LR+ = Sensitivity/(1 − Specificity)

Lower limit = exp
\[
\ln((nc2 \times a)/(nc1 \times b)) - z\sqrt{((a/(a \times nc1)) + (d/(b \times nc2)))} \quad \text{Upper limit} = \exp
\ln((nc2 \times a)/(nc1 \times b)) + z\sqrt{((c/(a \times nc1)) + (d/(b \times nc2)))}
\]

**Negative likelihood ratio**

*LR*+ = (1 – Sensitivity)/Specificity

Lower limit = \exp
\ln((nc2 \times c)/(nc1 \times d)) - z\sqrt{((a/(c \times nc1)) + (b/(d \times nc2)))} \quad \text{Upper limit} = \exp
\ln((nc2 \times c)/(nc1 \times d)) + z\sqrt{((a/(c \times nc1)) + (b/(d \times nc2)))}

* When calculating LR, if any cell of the 2 × 2 table contained the value of zero, 0.5 was added to all cells, to avoid creating the unlikely LRs of 0 or infinity (McGee, 2007).

**Equation used to calculate diagnostic odds ratio (ORs)**

Diagnostic ORs = (sensitivity / (1 - sensitivity))/((1 - specificity)/specificity)

**Statistical Formulae for pooling of proportions**

*Homogeneous sensitivity and/or specificity*

**Sensitivity:**

\[
\text{Sensitivity}_{pooled} = \frac{\sum_{i=1}^{k} a_i}{\sum_{i=1}^{k} (a_i + c_i)}
\]

whereby

\[ a = \text{true positives} \]
\[ c = \text{false negatives} \]
\[ i = \text{study number} \]
\[ k = \text{total number of studies} \]

with standard error:

\[
SE = \sqrt{\frac{p(1-p)}{n}}
\]

whereby

\[ p = \text{Sensitivity}_{pooled} \]
\[ n = \sum_{i=1}^{k} (a_i + c_i) \]
Specificity:

\[ Specificity_{pooled} = \frac{1}{k} \sum_{i=1}^{k} \frac{a_i}{\sum (a_i + c_i)} \]

whereby  
\( a = \) true negatives  
\( c = \) false positives  
\( i = \) study number  
\( k = \) total number of studies

with standard error:  
\[ SE = \sqrt{\frac{p(1-p)}{n}} \]

whereby  
\( p = \) Specificity_{pooled}  
\( n = \sum_{i=1}^{k} (a_i + c_i) \)