## PEER REVIEW HISTORY



This paper was submitted to the JNNP but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | [$^{123}$I]FP-CIT SPECT in suspected dementia with Lewy bodies: a longitudinal case study |
| **AUTHORS** | Siepel, Françoise; Rongve, Arvid; Buter, Tirza; Beyer, Mona; Ballard, Clive; Booij, Jan; Aarsland, Dag |

## VERSION 1 - REVIEW

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| **REVIEWER** | Nobili, Flavio<br>Clinical Neurophysiology, of Neurosciences, Ophtalmology and Genetics |
| **REVIEW RETURNED** | 21-Nov-2012 |

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| **GENERAL COMMENTS** | This is an extremely interesting manuscript dealing with SPECT of the Dopamine Transporter (DAT) in patients with possible/probable DLB, followed-up for 2-5 years. There are two main results. First, 'false' positive (FP) scans in patients with low scores on RBD, parkinsonism, cognitive fluctuations and hallucinations, are actually true positive scans, just they are positive very early in the course of the disease. Second, a few 'false' negative (FN) scans were found (6% of cases) and here the authors provide a very meaningful discussion on the possible reasons of this FN data. I have found this part of the discussion really very interesting and very clearly expressed. An example of good scientific thinking, let's say.<br>I just have some comments.<br>RBD demonstration requires videopolisomnography. By means of the Mayo sleep Questionnaire makes RBD probable but not verified. The more recent paper by Boeve et al (2011) showed a sensitivity of 98% but a specificity of 74% versus the gold standard of PSG. This should be acknowledged.<br>My major concern regards those 8 patients submitted to DAT scan with a suspicion of DLB but with low scores in ALL of the 4 cardinal symptoms of DLB, i.e., parkinsonism, RBD, hallucinations and fluctuations. Then, why (and how) DLB was suspected in those 8 patients? Can the authors explain further?<br>What was the impact of drug therapy on some main symptoms, such as fluctuations and hallucinations, at follow-up examination? We know that acetylcholinesterase inhibitors can have a substantial positive effect on these symptoms. Should we assume that they were not employed in any patient during the period of the study? (this would be difficult to believe…). At the end of the Discussion the authors say that 'some patients were treated with drugs such as antidepressants, antipsychotics, L-DOPA and antidementia drugs, and scanned while on medication, which may influenced the interpretation of the [123I]FP-CIT SPECT scans.' But even of clinical |

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| | assessment, I would say. Any comment?<br>A main limitation is that (semi-) quantitative analysis of DAT SPECT has not been carried out, which could have changed the results (for instance, reducing the number of FN cases), as previously shown just in DLB patients (Walker et al., JNNP 2007). Could the authors comment?<br><br>Minor<br>Methods<br><br>The following sentence is not very clear: please, rephrase it.<br>'Cut-off values on the scales to rate typical DLB were at the 9/10 level of the UPDRS-motor subscale and 0/1 for the other scales'<br><br>'Initial diagnosis of possible or probable DLB was made using clinical judgement.' According to the 2005 criteria published in Neurology?<br><br>'Missing values analysis with expectation-maximization algorithm was performed when scores at one of the four symptom scales was missing.' Since the classification of patients strongly relies on these scores, it would be useful to know in detail how many missing values and in how many patients the authors have 'extrapolated'.<br><br>The Discussion is a bit long and should be shortened.<br><br>References<br>Boeve BF, et al. Validation of the Mayo Sleep Questionnaire to screen for REM sleep behavior disorder in an aging and dementia cohort. Sleep Med. 2011 May;12(5):445-53. |

- The manuscript received a second and third review at the JNNP but the reviewer did not give permission for their comments to be published

## VERSION 1 – AUTHOR RESPONSE

**RBD demonstration requires videopolisomnography. By means of the Mayo sleep Questionnaire makes RBD probable but not verified. The more recent paper by Boeve et al (2011) showed a sensitivity of 98% but a specificity of 74% versus the gold standard of PSG. This should be acknowledged.**
We agree and added a brief comment on this in the Discussion.
**My major concern regards those 8 patients submitted to DAT scan with a suspicion of DLB but with low scores in ALL of the 4 cardinal symptoms of DLB, i.e., parkinsonism, RBD, hallucinations and fluctuations. Then, why (and how) DLB was suspected in those 8 patients? Can the authors explain further?**
As stated above, the selection for Datscan was not standardized. Thus some may have been referred for only very minor DLB-symptoms, autonomic symptoms, or a non-amnestic cognitive profile.
**What was the impact of drug therapy on some main symptoms, such as fluctuations and hallucinations, at follow-up examination? We know that acetylcholinesterase inhibitors can have a substantial positive effect on these symptoms. Should we assume that they were not employed in any patient during the period of the study? (this would be difficult to believe…). At**
**the end of the Discussion the authors say that 'some patients were treated with drugs such as antidepressants, antipsychotics, L-DOPA and antidementia drugs, and scanned while on medication, which may influenced the interpretation of the [123I]FP-CIT SPECT scans.' But even of clinical assessment, I would say. Any comment?**

We agree that drug treatment might influence the clinical course, and this is acknowledged in the Discussion.

**A main limitation is that (semi-) quantitative analysis of DAT SPECT has not been carried out, which could have changed the results (for instance, reducing the number of FN cases), as previously shown just in DLB patients (Walker et al., JNNP 2007). Could the authors comment?**

In this study, a systematic visual analysis was performed by an nuclear medicine specialist who has much experience in the interpretations of DAT SPECT scans and was blinded to the clinical data. We have chosen to analyze the images visually because the scans were acquired on different camera systems (see MM section manuscript). It is well known that semi-quantitative analyses of FP-CIT SPECT images are dependent on the camera system used (Varrone et al., EJNMMI 2013). On the other hand, visual analysis is the standard clinical practice used for evaluation of [123I]FP-CIT SPECT

in most departments. Even more important, in previous studies, this approach has been used usefully, and showed to be as accurate as quantitative techniques to differentiate abnormal from normal scans (McKeith et al., Lancet Neurol 2007). Nevertheless, we now added to our manuscript this potential limitation.

**Minor**

**Methods**

**The following sentence is not very clear: please, rephrase it.**

**'Cut-off values on the scales to rate typical DLB were at the 9/10 level of the UPDRS-motor subscale and 0/1 for the other scales'**

We agree with the reviewer that this sentence could be more clear by rephrasing (see manuscript).

**'Initial diagnosis of possible or probable DLB was made using clinical judgement.' According to the 2005 criteria published in Neurology?** Yes, the reference is added.

**'Missing values analysis with expectation-maximization algorithm was performed when scores at one of the four symptom scales was missing.' Since the classification of patients strongly relies on these scores, it would be useful to know in detail how many missing values and in how many patients the authors have 'extrapolated'.**

This extrapolation information about the missing values is added to the manuscript (Results section).