Correspondence

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Lack of evidence to support the conclusion that dopaminergic imaging is useful to diagnose mild cognitive impairment with Lewy bodies

We read with interest Roberts et al's paper on dopaminergic imaging as a biomarker for mild cognitive impairment with Lewy bodies (MCI-LB).[1] However, we believe that the authors' conclusion that dopamine imaging is useful when Lewy body disease is suspected in a patient with MCI is not supported by the data presented. This otherwise well-designed and conducted study has issues that we commonly see in our Cochrane Dementia reviews of dementia tests. We highlight the potential biases here to raise the visibility of these issues in the dementia test accuracy community.

First, unquantifiable bias may be introduced by the reference standard (probable MCI-LB assessed using recent research criteria[2]). Imperfect reference standards are common in dementia research.[3] However, for Lewy body disease, in particular clinical diagnosis (that is not informed by imaging) is problematic as there are studies of dopamine imaging versus neuropathology that suggest the imaging is more accurate than clinical diagnosis.[4,5] It is axiomatic that a test cannot be assessed against a reference standard that is less accurate than the new test itself.

Another common issue in dementia test accuracy is around the generalisability of the populations studied. Here we agree with the authors that the place of dopaminergic imaging in the clinical pathway is when Lewy body disease is clinically suspected but uncertain. The study population seems appropriate, although 36/144 patients already met criteria for probable Lewy body disease when recruited. It is difficult to see how imaging adds value to the assessment of these patients. In the primary analysis, the authors exclude the 26 patients with the most uncertain diagnoses at follow-up. This approach risks introducing spectrum bias and inflating accuracy estimates. If we recalculate test accuracy limited to the 108 patients for whom the diagnosis of Lewy body disease was clinically uncertain at baseline, we find sensitivity of 60% and specificity of 83% for dopaminergic imaging. If we include the 36 patients meeting criteria for probable Lewy body disease at baseline, on the grounds that at least some of them might not have been identified in less specialist services, sensitivity is increased to the authors' estimate of 66% but specificity remains lower at 83%.

Sensitivity and specificity metrics can seem abstract and clinicians will want to know whether the tests have value in their practice. The accuracy figures that would demonstrate the dopamine imaging to be clinically 'useful' are not prespecified, but both our figures and the author's own accuracy estimates suggest substantial potential for misclassification. The relatively low sensitivity means that negative dopamine imaging in a patient with MCI and suspicion of Lewy body disease cannot be relied upon to exclude the diagnosis for the purposes of treatment (for example with antipsychotics for psychiatric symptoms) or for research inclusion (for example

Alzheimer's disease therapy trials); as many as half of negative results could be wrong.

We believe that imaging and other biomarkers have a useful role in dementia diagnosis. However, for this study, because of the biases described, the recommendations around adopting dopamine imaging in clinical practice are not supported.

Declaration of interest

1 Roberts G, Donaghy P, Lloyd J, Durcan R, Petrides G, Colloby S, et al. Accuracy of dopaminergic imaging as a biomarker for mild cognitive impairment with Lewy bodies. *Br J Psychiatry* 2021; **218**: 276–82.

2 McKeith IG, Ferman TJ, Thomas AJ, Blanc F, Boeye BF, Fujishiro H, et al. Research criteria for the diagnosis of prodromal dementia with Lewy bodies. *Neurology* 2020; **94**: 743–55.

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Authors' response

We thank Dr McCleery & Dr Quinn, from the Cochrane Dementia and Cognitive Improvement Group, for their interest in our recent paper on the accuracy of dopaminergic imaging as a biomarker for mild cognitive impairment with Lewy bodies (MCI-LB).[1] However, we disagree with their argument that we have not demonstrated [123I]N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane (123I-FP-CIT) to be useful in MCI-LB, because of biases arising from an imperfect reference standard and exclusion of patients with uncertain cases.

We agree that it is challenging to design a perfect diagnostic accuracy study in the field of neurodegenerative diseases, and that many studies, including our own, have limitations. However, we discuss these limitations in the paper and they do not detract significantly from our findings. A recent systematic review used Bayesian methods to adjust for the lack of neuropathological reference standard in most studies, finding similar accuracy results for the diagnosis of clinical dementia with Lewy bodies (DLB) with 123I-FP-CIT before and after adjustment.[2] Our results of moderate sensitivity and high specificity are valid and demonstrate that a positive (abnormal) dopaminergic imaging result in suspected MCI-LB is indeed useful in supporting the diagnosis. We agree that a negative result does not exclude MCI-LB, but it is now well-known that a normal scan does not completely exclude DLB in patients with established dementia. Clinicians recognise that a test with sensitivity estimated at 66% is not going to identify all cases.

Drs McCleery & Quinn are, of course, correct that a clinical diagnosis of MCI-LB is an imperfect reference standard, but what is their alternative? The gold standard of post-mortem pathology diagnosis is not feasible for early-stage neurodegenerative studies. In our study we sought to make our clinical diagnoses as reliable

as we possibly could by incorporating cardiac metaiodobenzylguanidine (mIBG) findings, where available, and using a panel of three old-age psychiatrists all specialising in Lewy body disease. Our participants have all been invited to donate to our tissue resource on death and in time we intend to update the results of this study with pathological diagnoses as the reference standard, where available.

Optimising our reference standard was our rationale for excluding patients with an uncertain follow-up diagnosis of possible MCI-LB. We are aware that excluding patients with the most uncertain cases risks partial verification bias,[3] but in this case we strongly feel that the improvement to the quality of our clinical diagnoses and thus our reference standard outweighs the risk of overestimating sensitivity and specificity. On balance, our results are likely to be a worse estimate of the true diagnostic accuracy with the uncertain cases included than with them excluded. We continue to follow these participants up, but feel it is inappropriate to group them as having MCI-LB at present for the purposes of diagnostic accuracy assessment. This prospective review is the key to making our reference clinical diagnoses as accurate as possible.

We did not aim to image only patients with uncertain diagnoses at baseline, although we agree this would be a very valuable future study. Rather, we aimed to end up with two reasonably definitive groups of patients at follow-up – those who we could be as confident as possible do have MCI-LB and those who we are confident do not. In the absence of neuropathological verification, it is only by selecting patients with probable diagnoses that we can usefully test the accuracy of baseline dopaminergic imaging in MCI-LB.

Declaration of interest

References

1 Roberts G, Donaghy P, Lloyd J, Durcan R, Petrides G, Colloby S, et al. Accuracy of dopaminergic imaging as a biomarker for mild cognitive impairment with Lewy bodies. *Br J Psychiatry* 2021; **218**: 276–82.

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