Reviewer’s report

Title: Sub-clinical abnormalities detected by PET/MRI in household tuberculosis contacts

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Reviewer: Hanif Esmail

Reviewer's report:

The authors present findings of PET/MRI conducted in 30 adult household contacts of 20 index cases with pulmonary tuberculosis. The aim of the study is to identify evidence of subclinical disease activity related to TB which may not be visible on CXR. The study was conducted in Singapore where the background rate of LTBI is 4-30% hence it is not clear for what proportion this would represent primary infection. The authors identified PET/MRI abnormalities (within either lung parenchyma or mediastinal/hilar LN) in 40% of contacts (40% of which were IGRA positive - there was no clear relationship between IGRA status and PET/MRI abnormality). While the authors acknowledge the clinical significance of these abnormalities are uncertain they conclude that the abnormalities most likely relate to subclinical TB disease activity, that such individuals may be at higher risk of disease progression and that PET/MRI may be a useful research tool in this setting.

Although this is an exciting area of research with the potential to provide insight into disease progression in TB, I am not convinced the authors conclusions are justified by the findings they present or that the imaging findings necessarily relate to TB. In order to have greater confidence in interpreting the findings the authors would need to either have a control group of similar individuals who were not household contacts, show dynamic change in lesions with treatment or relate findings to hard endpoints such as clinical disease development. As a result I do not think the study merits publication at this stage. Major issues I have with the study are outlined below.

1. It is not clear to me how systematic the study methodology was. Why were the contacts referred? Was it for routine contact investigation or because there was some concern from referrer about possibility of active TB or was it specifically for the study? Over what period did the study take place? How many contacts were seen in the unit over that period? This is important as it will help to understand how generalisable the findings are and whether there may be any bias in participant selection.

2. The authors report various abnormalities which they consider to be relevant but these have not really been systematically analysed or critically assessed.

   a) Of note 3 patients have FDG uptake within the parenchyma with no underlying structural abnormality on MRI. Although MRI is less widely used than CT, not identifying an anatomical abnormality that relates to the FDG uptake is of concern as such abnormalities have been reported to be artefacts (possibly related to microembolisation of injected FDG) and are often not visible on repeat imaging. If the authors feel this relates to reduced sensitivity for
parenchymal lesions of MRI in comparison to CT, it would be difficult to make the case that PET/MRI is a preferable research tool in comparison to PET/CT (Low sensitivity of MRI for parenchymal lesions however seems unlikely as they report on 3mm nodules in other scans)

b) The authors note that the predominant abnormality is FDG uptake in mediastinal and hilar lymph nodes and assert that this is likely to be related being a TB contact, citing a study from Japan in which 155,456 healthy people scanned with PET/CT. This study has very limited detail about the definitions used to determine abnormalities and the aim of it was not to specifically establish FDG-PET findings in lymph nodes of healthy people. A key issue with PET imaging of lymph nodes especially the mediastinal and hilar LN is the threshold at which something is determined to be abnormal. From the manuscript it appears that none of the lymph nodes were abnormal in size (>1cm) as there was no reported lymphadenopathy solely on MRI. The criteria for abnormality is therefore, visually increased FDG uptake within LN in comparison to background (the only SUVmax cut off provided is 0.95 for parenchyma which is far too low for lymph nodes). In a study (Kwan et al Anticancer Res. 2001) in which 179 healthy controls underwent FDG-PET/CT 28% were found to have visually increased FDG uptake within hilar lymph nodes however none were found to have SUVmax > 3. Using a SUVmax cut off of 3 to increase confidence that LN has abnormal uptake would mean that only 2 of the 6 patients reported as abnormal were likely to be so.

c) The authors report isolated nodules on PET/MRI as being significant abnormalities. Nodules are very common findings and the authors also do not report the smoking history of the participants. In addition 2 of the nodules were <=6mm and had either no or faint FDG uptake which makes me doubt their significance. In any case primary infection with TB (and not disease) can also result in nodules.

d) The authors report bilateral apical scarring of the lungs in 1 participant. This is only of interest if the participant has no history of TB treatment at any point (the only exclusion was within the last year). FDG uptake is commonly reported in previously treated TB (see Malherbe et al Nat Med 2016)

e) All in all of the 12 participants reported as having significant abnormalities I can only be confident that that scans in 2 out of the 12 were abnormal and not within normal limits (or related to alternative benign pathology). This is the reason that a well matched control group or some other way to increase confidence in findings is important (clinical endpoint or treatment response).

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

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