Reviewer’s report

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

Version: 2  Date: 31 Jul 2018

Reviewer: Hanif Esmail

Reviewer's report:

Many thanks for inviting me to review the manuscript again. It is well written and has been improved with revision but I still have the following concerns,

1. I do not think the term subclinical disease can reasonably be used in the title or manuscript. The term subclinical disease in tuberculosis is becoming increasing well understood and well defined as representing a state of failure of containment of the latent infection, where evidence of disease is visible but without causing subjective symptoms (see recent review Drain et al CMR 2018). Though disease at this stage can be halted, importantly it is associated with high risk of progression to symptomatic disease. Many of the lesions described do not have strong evidence in either imaging or autopsy literature that they represent an early stage of disease and hence I do not think it reasonable to state that the abnormalities found represent subclinical disease. "Subclinical abnormalities detected by PET/MRI in household TB contacts" is a more faithful title.

2. The authors make the case that PET/MRI could be used for biomarker discovery, but it is critical that the imaging phenotype is understood in relation to outcome or pathological process which this study does not shed light on. Fuzzy phenotypes are not helpful for biomarker discovery. I am still concerned by the 3 participant with PET abnormalities not identified on MRI. It is not clear at all what the significance of this is or how it might relate to TB pathology (they are also not included in the figure which they should be). Arguing that lesion may be too small to be visible but excluding lesion<6mm with minimal uptake (presumably SUVmax > 0.95) is slightly contradictory particularly as these lesions have fairly low uptake (SUVmax 1.3-2.8). Such lesions are not infrequently described in the literature (see Tokmak World J Nucl Med. 2013 Jan-Mar; 12(1): 38-40.) the evidence is that they usually disappear on repeat imaging (I am not sure if either of these 3 participants has had repeat imaging).

3. The authors make the point that the PPV of IGRA is low however the NPV is extremely high (99%), TB very rarely develops in immune competent HHC with negative IGRA or TST. It is therefore of concern that >50% of those with abnormal PET/MRI had a negative IGRA, of note all 3 of the participant with FDG uptake without parenchymal lesions had negative IGRA which again makes me suspicious of the significance of this. On the whole I would be inclined to advice that these 3 lesions not be included.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

No

Are the conclusions drawn adequately supported by the data shown?
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No

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