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Title: Refractory very-early onset inflammatory bowel disease associated with Cytosolic Isoleucyl-tRNA synthetase deficiency: A case report

Authors: Andrew Fagbemi, WG Newman, SG Tangye, Stephen Hughes, Edmund Cheesman, Peter Arkwright

Point-by-point responses to Reviewers comments

The authors are grateful for the very helpful comments of the two reviewers. Specific point-by-point responses are provided below.

Reviewer #1:

This MS focuses on a specific case of early onset gut inflammation and illustrates the functional aspects of the genetic cause in this case, expanding our understanding of potential monogenic causes of gut inflammation SPECIFIC COMMENTS

1. The authors have variously used the terms early-onset IBD and very early-onset IBD. these should be consistent.

Response: The term "very early-onset IBD" has now been used consistently throughout the manuscript.

2. In the case history section, several verbs are given in present tense (has and remains). These should be past tense (had and remained).

Response: Tense has now been changed to past tense as suggested in the case history section.

3. Abbreviations should be explained as per standard fashion (TNF for example).

Response: Abbreviations have now been explained.

Reviewer #2:

This is a very interesting case report - presenting evidence that a deficiency in cytosolic ARS can lead to liver failure and early onset, unresponsive IBD. My comments: The paper is well written, the figures are illustrative and clear and overall it is very pleasant to read.

1. the fact that the patient was positive for a ARS mutation and negative for IBD associated genetic variants does not exclude that the patient could have sporadic IBD

(though it is not likely). I would mention this somewhere in the discussion and mitigate a little the conclusions.

Response: Supportive evidence from reports of other patients with the same genotype-phenotype would indeed be helped to definitively confirm the association. This has now been emphasized in the first paragraph of the Discussion section.

2. Throughout, the authors discuss "IBD" but never mention Crohn's or UC. Is it because pathology could not distinguish them? Have the authors tested the boy for small bowel disease? ANCA/ASCA? Family history of IBD?

Response: There were no granuloma to suggest Crohn's, although the distribution of the inflammation in the cecum and the pancolitis was similar to that seen in UC. These additional details have now been added to the Case Report description.

3. It is unclear why the boy was included in the genome project. Because of the clinical suspicion? It should be mentioned.

Response: In view of the very early-onset of the disease and its poor response to immunosuppressive medication, an underlying genetic cause was considered likely, This statement has now been added to the Case Report description.

4. It is also unclear why the authors tested those particular cytokines. At minimum I would comment on the results which are a bit puzzling since IL-10 should be lower and TNF should be higher than in controls (but a number of explanations are plausible of course).

Response: The cytokine array covered Th1, Th2, Th17 and Treg pathway cytokines that may be deranged in IBD. This has been clarified in the Case Report description. Possible explanation for the raised IL-10 in the patient is now provided in the second paragraph of the Discussion section.