

Peer Review File

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Reviewer Comments

Importance of Differentiating Cystic Fibrosis from Inflammatory Bowel Disease

This is a case presentation of a late diagnosis of CF. The clinical presentation would have raised alarm bells of CF had this presented in a different geographical context. As this occurred in a country where CF diagnosis is infrequent, this is worthy of consideration for publication. I have the following comments/questions/suggestions:

Introduction

Comment 1. “However, abdominal pain, diarrhea, and failure to thrive are common clinical manifestations of CF and can lead to a range of gastrointestinal complications”. Suggest refer to the following publication that attempts to address these symptoms in CF, and also add to your Discussion section (Bolia R, et al. Practical approach to the gastrointestinal manifestations of cystic fibrosis. *J Paediatr Child Health*. 2018 Jun;54(6):609-619).

Reply 1: Thank you for your comment. We agree and have revised according to your comment.

We have provided a marked file by using a different color of text to show the changes.

Changes in the text: We have added the publication as reference 4 (see Page 3, line 9 and Page 6, line 25)

Comment 2. “...can lead to a range of gastrointestinal complications, including chronic inflammation, gut microbiota disruption, and gastrointestinal malignancies”. This statement should cite the following publication that attempted to link all these 3 issues together. Coffey MJ, Nielsen S, et al. Gut Microbiota in Children With Cystic Fibrosis: A Taxonomic and Functional Dysbiosis. *Sci Rep*. 2019 Dec 9;9(1):18593.

Reply 2: Thank you for your comment. We agree and have revised according to your comment.

Changes in the text: We have added the publication as reference 5 (see Page 3, line 9)

Comment 3. “Therefore, when evaluating pediatric patients suspected of chronic intestinal inflammation, a high index of suspicion for CF is required...”

The differentials for symptoms of abdominal pain, diarrhea and FTT are broad and may include conditions other than intestinal inflammation.

Reply 3: Thank you for your comment. We agree and have revised according to your comment.

Changes in the text: We have modified our text as advised (see Page 3, line 10)

Discussion

Comment 4. “Reduced transport of chloride ion results in ion imbalance and reduced immunity.” This statement is not entirely accurate. Please refer to and cite the following which summarises the altered intestinal milieu in CF due to a variety of factors

including loss of bicarbonate secretion and the resultant inspissated mucus: Ooi CY, Durie PR. Cystic fibrosis from the gastroenterologist's perspective. *Nat Rev Gastroenterol Hepatol*. 2016 Mar;13(3):175-85.

Reply 4: Thank you for your comment. We agree and have revised according to your comment.

Changes in the text: We have added the publication as reference 6 and modified our text as advised. (see Page 6, line 22-24)

Comment 5. “FC is thought to correspond with severity of inflammation; however, the results of a previous study indicate this may not be the case in CF (10).”

This statement is arguably inaccurate.

Elevations in faecal calprotectin has been shown to correlate clinically

- FC correlates with growth impairment: Intestinal inflammation and impact on growth in children with cystic fibrosis.
Dhaliwal J, Leach S, et al. *J Pediatr Gastroenterol Nutr*. 2015 Apr;60(4):521-6.
- FC associated with hospitalisation: Gastrointestinal Factors Associated With Hospitalization in Infants With Cystic Fibrosis: Results from the BONUS Study.
Sathe M, Huang R, et al.
J Pediatr Gastroenterol Nutr. 2021 May 18.
- FC associated with more symptoms and worse quality of life: Increased Fecal Calprotectin Is Associated with Worse Gastrointestinal Symptoms and Quality of Life Scores in Children with Cystic Fibrosis.
Beaufils F, Mas E, et al. *J Clin Med*. 2020 Dec 17;9(12):4080.

Reply 5: Thank you for your great comment. We agree and have revised according to your comment.

Changes in the text: We have added the publication as reference 12,13 and modified our text as advised. (see Page 7, line 12-14)

Comment 6. “...however, the results of a previous study indicate this may not be the case in CF (10)”

As per above comment, this part of the sentence above does not make sense or not written very clearly. Suggest remove or edit.

Reply 6: Thank you for your comment. We agree and have revised according to your comment.

Changes in the text: We have removed the sentence. (see Page 7, line 12)

Comment 7. Lastly, a stronger discussion on issues related to a late diagnosis of CF in Korean populations need to be discussed further. The story is similar to those reported in Chinese and Japanese populations.

Reply 7: Thank you for your comment. We agree and have revised according to your comment.

Changes in the text: We have modified our text as advised (see Page 7, line 20-24)