

Peer Review File

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Reviewer A

The manuscript "Food protein-induced enterocolitis presenting after necrotizing enterocolitis in a preterm neonate: a case report" presents an interesting case of FPIES. The presented information is not new about FPIES, but a valuable addition to the literature. The manuscript is concise. The tables are helpful. The discussion is short and referencing the most important publications on the topic. The study would benefit from a thorough check of the English language.

Some revisions needs to be done by the authors:

- You should add “syndrome” into “Food protein-induced enterocolitis”. Therefore, “Food protein-induced enterocolitis syndrome (FPIES)” should be used throughout the manuscript.

We apologize for the error, and the correction has been made in the revised manuscript (see page 1 line 1; page 2 line 1,5,20; page 3 lines 4,16, 21,22, et)

Abstract:

- You should define the abbreviations upon first use. For example, you should define “NICU”.

We apologize for the error, and the correction has been made in the revised manuscript. (page 1 line 23, page 7 line 10)

Please define “NEC” and “DOL” after first use. And try to be consistent with the abbreviations throughout the manuscript.

We apologize for the error, and the correction has been made in the revised manuscript.

Define NEC, We have modified our text as advised (page 1 line 23, page 2 lines 2, 5, 7, 9, 12, 16, 20, page 3 lines 9,10, 11, 13, 22, pages 4-10)

Define DOL, we have modified our text as advised (page 2 lines 10, 12, 14); page 4, lines 5, 22)

- “When bloody stools occur in a very low-birth weight infant cared for in NICU”. Please delete “care for in NICU”

We apologize for the error, and the correction has been made in the revised manuscript. (page 1, line 22)

- “Here, we report the case of a very low-birth weight infant born at 28 weeks of gestational age with recurrent episodes of bloody stools with cow’s milk or breast milk fortified with milk feeding on DOL 29, 46, and 54 after NEC recovery on DOL 20.” please rephrase

We apologize for the error, and the correction has been made in the revised manuscript (page 2, lines 7-10)

- “A male very low-birth weight neonate born at 28 weeks of gestational age presented with recurrent episodes of bloody stools after recovery from early-onset NEC on day of life 7. After recovery of NEC on day of life 20, the baby developed three recurrent episodes of bloody stools with cow’s milk or breast milk fortified with milk feeding on day of life (DOL)29, 46, and 54.” This paragraph is a repetition of the previous one.

Thank you for your suggestion, and the necessary corrections have been made in the revised version.

We added some data (see Page 2 lines 11-14)

- “He was suspected of having recurring NEC.” please replace “recurring NEC” with “recurrent episodes of NEC”

We apologize for the error, and the correction has been made in the revised manuscript (page 2, lines 15-16)

Introduction:

- “A subset of patients can also present with gagging, food refusal 63 and irritability”. Please replace “A subset of patients” with “Some”

Thank you for your suggestion, and the correction has been made in the revised manuscript. (page 3, line 20)

Case presentation”

- You should be consistent with your terms. You should use “infant” instead of using “neonate” throughout your manuscript.

Thank you for your suggestion, and the necessary corrections have been made in the revised version (Page 2, lines 4, 8, 11, 22; page 3 line 7; page 4 line 14; page 8 lines 1, 2, 3, 21; page 7 lines 13, 16, 19)

- Please define the abbreviation “G1P1”

Thank you for your suggestion, and the necessary corrections have been made in the revised version (page 4 line 14)

- “The baby was delivered through a cesarean section with a birth weight of 1240 g” what was the indication for the section? Was she in labour?

We apologize for the error, and the necessary corrections have been made in the revised version (Page 4 line 17)

cesarean section

- “The baby was treated for respiratory distress failure at birth” what is “respiratory distress failure”? do you mean respiratory distress syndrome (RDS)?

Yes, the baby had respiratory failure after birth and he was diagnosed with respiratory distress syndrome. We have modified our text (page 4 line 20)

- “On DOL 7, the baby developed formula retention.” can you explain what is “formula retention”?

Thank you for your suggestion, formula retention refers to increased gastric residual, and the necessary corrections have been made in the revised version (page 5 line 3)

- “The baby was made nil per os..” should be replaced with “feeds were stopped”

We have modified our text as advised (Page 5 line 9)

- “The patient returned home after 60 days of hospitalization, and a change to expressed mother’s milk resulted in nonrecurrence of the symptoms.” Please replace “returned” with “discharged”. Do you mean FPIEs resolved completely? Can you explain this in more detail? Did the baby have a follow up?

Thank you for your suggestion, and the necessary corrections have been made in the revised version (page 7 line 4-5)

Discussion

- “When bloody stools occur in a prematurely born infant cared for in the NICU, NEC is a prime consideration, although food allergy-induced enterocolitis can be causative and difficult to distinguish from NEC.” This paragraph is a word for word repetition of one in your abstract.

We apologize for the error, and the necessary corrections have been made in the revised version (page 7 line 7-14)

- “The risk factors for developing FPIE are an immature immune system, altered intestinal permeability, and genetic susceptibility in combination with sensitizing foods.[11] Previous exposure to CMA and, in many cases, to CMA transferred via fortifier or breast milk is a major risk factor in neonates. The immature intestine is exposed to multiple factors, such as ischemic injuries and food restrictions, which can damage the gut epithelium and make it more vulnerable to food antigens, inducing an inflammatory mucosal response mediated by T cells. According to this report, we suppose that premature neonates are at risk for CMA and bovine-based fortifiers, especially after intestinal damage with NEC.” This section is quite vague, shallow and lacks a clear discussion. I would suggest to rephrase/rewrite it.

Thank you for your suggestion, and we agree with the reviewer's point of view, and the necessary corrections have been made in the revised version. (page 8 line 8-18)

- “In this case report, we reconfirmed an apparent increase in eosinophils in patients with FPIE occurring subsequent to NEC.” please replace “reconfirmed” with “confirmed”

We apologize for the error, the necessary corrections have been made in the revised version (page 8 line 21)

- “There was also a report that immature infants with early persistent blood eosinophilia were at high risk during NEC convalescence” what does “immature” mean? Preterm infants? please be consistent with the terms.

Thank you for your suggestion, immature infants “refers to “preterm infants”, the necessary corrections have been made in the revised version (page 9 line 3)

- “Most FPIE infants are well appearing without abdominal tenderness.” Please add references

We apologize for the error. In our case, infant with FPIE was well appearing without abdominal tenderness and the bowel sounds were active. But when we check the reviews of FPIES, we found gastrointestinal symptoms, including vomiting and abdominal distention, were also common in neonates, so the necessary corrections have been made in the revised version (page 10 lines 3-6)

The study would benefit from a thorough check of the English language.

We feel very sorry for our so poor English writing. Therefore, we have checked language once more and corrected the errors before re-submission.

Reviewer B

General formatting feedback (these are all minor and very easy to edit)

- In some parts of the case report the front colour is red (lines 94, 95, 108, 109), grey (lines 121-122) and the rest is in black. I would use black colour font throughout.

We apologize for the error., We have modified our text as advised (page 4 lines 5,6, 20, 22; page 5 line 7; page 6 line 1,3)

- For ‘Case Reports’ the journal allows a maximum of 20 references but you have listed 21. I am afraid you will need to remove a reference.

We apologize for the error, we have modified our text as advised.

- Line 21 the abbreviation ‘NICU’ is used but hasn’t been defined, i.e. Neonatal Intensive Care Unit. This is a requirement of the journal.

We apologize for the error, the necessary corrections have been made in the revised version (page 1 line 23; page 7, line 7)

- Lines 21-22 is the first time you write ‘necrotizing enterocolitis’ but you don’t give the abbreviation until line 23. I would give the abbreviation (NEC) the first time you write ‘necrotizing enterocolitis’. Then use the abbreviation, NEC, for the remaining sections of the abstract.

We apologize for the error, and the correction has been made in the revised manuscript. (page 1 line 23, page 2 lines 2, 5, 7, 9, 12, 16, 20, page 3 lines 9,10, 11, 13, 22, pages 4-10)

- Line 22 need a space between ‘enterocolitis’ and ‘(FPIE)’

We apologize for the error, and the necessary corrections have been made in the revised version (page 2 line 1)

- Line 34 need a space between ‘(DOL)’ and ‘29’

We apologize for the error, and the necessary corrections have been made in the revised version (page 2 line 14-15)

- Line 36 the abbreviation ‘CRP’ is used but hasn’t been defined

We apologize for the error, and the necessary corrections have been made in the revised version (Page 2 line 13)

- Line 23 you define and given the abbreviation for necrotizing enterocolitis (NEC). On lines 38-39 you write necrotizing enterocolitis in full; this can be abbreviated.

We apologize for the error, and the necessary corrections have been made in the revised version (page 2 line 2, 20)

- I would place the full stop (.) after the reference and not before. For example, on lines 53-54 the full stop is before the reference ‘...colon and intestine.[2] As NEC progresses,’ but it should be after the reference ‘...colon and intestine [2]. As NEC progresses’

We apologize for the error, we have made necessary corrections in the revised version

- It is recommended to avoid using the same word or abbreviation that both ends and starts consecutive sentences. On line 51 NEC is used to end and start consecutive sentences.

Thank you for your suggestion, and the necessary corrections have been made in the revised version (page 3 line 9)

- Line 59 you need a space between ‘enterocolitis’ and ‘(FPIE)’

We apologize for the error, and the necessary corrections have been made in the revised version (page 3 line 16)

- I would add the sentence ‘We present the following article in accordance with the CARE reporting checklist’, that is currently on line 73, to the end of the third paragraph on line 72.

Thank you for your suggestion, and the necessary corrections have been made in the revised version (page 4 line 7-8)

- Line 81 the abbreviation ‘G1P1’ is used but hasn’t been defined

We apologize for the error, and the necessary corrections have been made in the revised version (page 4 line 14)

- Line 85 need to insert a comma after ‘minutes’ and before ‘respectively’

We apologize for the error, and the necessary corrections have been made in the revised version (page 4 line 19)

- Line 94 the abbreviation ‘WBC’ is used but hasn’t been defined

We apologize for the error, and the necessary corrections have been made in the revised version (page 5 line 6)

- I would write ‘figure’ with a capital ‘F’ (lines 95, 109)

We apologize for the error, and the necessary corrections have been made in the revised version (page 5 line 8, page 6 line 2)

- Line 98 I would write ‘24 h’ as ‘24 hours’. Both styles count as two words.

We apologize for the error, and the necessary corrections have been made in the revised version (page 5 line 12)

- Line 119 I would write ‘Stool’ with a small ‘s’

Thank you for your suggestion, and the necessary corrections have been made in the revised version (page 6 line 8)

- Line 119 you state “...because it’s not available in our section.” Section is not a common phrase. Do you mean department or hospital?

Yes, we mean hospital, and the necessary corrections have been made in the revised version (page 6, line 16)

- Line 124 the abbreviation ‘FPIE’ is used but hasn’t been defined in the body of the paper

We apologize for the error, and the necessary corrections have been made in the revised version (page 3 line 16)

- Lines 141-142: ‘The most common food allergy in infants is to cow's milk allergy (CMA)’ I would remove ‘to’ in this sentence so that it reads ‘The most common food allergy in infants is cow's milk allergy (CMA)’

Thank you for your suggestion, and the necessary corrections have been made in the revised version (page 7 line 16)

- Line 143, I think you have an extra space between ‘symptoms’ and ‘such’

We apologize for the error, and the necessary corrections have been made in the revised version (page 7 line 17)

- Line 145, I think you have an extra space between ‘of’ and ‘FPIE’

We apologize for the error, and the necessary corrections have been made in the revised version (page 7 line 19)

- Line 147, you have written Japan in lower case, all countries should be spelt with the first letter in capitals. So ‘japan’ should be ‘Japan’

We apologize for the error, and the necessary corrections have been made in the revised version (page 8 line 2)

- Lines 172-173: It is recommended to avoid using the same word or abbreviation that both ends and starts consecutive sentences. I would change “Eosinophils might be involved in the inflammatory process in FPIE. FPIE was associated with eosinophilic inflammation on histology of colonic biopsy in some cases.” to something like “The inflammatory process in FPIE may involve eosinophils. FPIE was associated with eosinophilic inflammation on histology of colonic biopsy in some cases.”

Thank you for your suggestion, and the necessary corrections have been made in the revised version

(page 9 line10-12)

- On line 93 you wrote ‘C-reactive protein (CRP)’ and continue to use the abbreviation CRP up to line 186 when you write ‘C-reactive protein levels’. You should continue to use the abbreviation CRP here too

We apologize for the error, and the necessary corrections have been made in the revised version (page 10 line 6)

Feedback on the case report

- I am a little confused by lines 154-156 “Previous exposure to CMA and, in many cases, to CMA transferred via fortifier or breast milk is a major risk factor in neonates”. Do you mean “Previous exposure to cow’s milk and, in many cases, to cow’s milk transferred via fortifier or breast milk is a major risk factor for neonates to develop CMA”? I would disagree that maternal diet, involving cow’s milk, would increase her infant’s risk for CMA (see: A. Muraro S. Halken S. H. Arshad K. Beyer A. E. J. Dubois G. Du Toit P. A. Eigenmann K. E. C. Grimshaw A. Hoest G. Lack L. O’Mahony N. G. Papadopoulos S. Panesar S. Prescott G. Roberts D. de Silva C. Venter V. Verhasselt A. C. Akdis A. Sheikh on behalf of EAACI Food Allergy & Anaphylaxis Guidelines Group and <https://www.aaaai.org/conditions-and-treatments/library/allergy-library/prevention-of-allergies-and-asthma-in-children>)

Yes, we very much agree with your point, it’s recommended not to restrict a mother’s diet of milk while breast-feeding, when a child is otherwise well. And it’s supposed least likely to trigger an allergic reaction. As suggested in international consensus guidelines, a handful of case reports describe allergen transmission and acute or chronic FPIES reactions attributed to breast milk, this is thought to be an exceptionally rare occurrence, and the manipulation of the maternal diet while breastfeeding an infant with FPIES remains highly controversial. So, we have made corrections in the revised version (page 8 line 8-18)