

Peer Review File

Article information: <https://dx.doi.org/10.21037/tp-21-121>

Reviewer A

Comment 1: There is room for grammatical improvements throughout the manuscript.

Reply 1: We employed an English-language editing service, to polish our wording throughout the manuscript.

Comment 2: “Although general expert consensus in the literature recommends the administration of the anti-epileptic drugs (AED) or anticonvulsive drugs, but it is in vain for most FIRES.”- reference needed

Reply 2: The relevant reference has been added into the revised manuscript.

Changes in the text: [7] Sculier C, Gaspard N. New onset refractory status epilepticus (NORSE) [J]. *Seizure* 2019, 68:72-78. (see Page 13, line 236)

Comment 3: levels are low in the fasting state, thus, “the brain utilizes fats as the source of energy in this instance”- reference needed

Reply 3: The relevant reference has been added into the revised manuscript.

Changes in the text: [13] Haleema A, Qudsia UK, Natasha N, et al. Epileptic seizures [J]. *Discoveries (Craiova)* 2020, 8(2): e110. (see Page 14, line 248-249)

Comment 4: The author needs to discuss the CRP, WBC, and temperature data. Why the CRP level and WBC counts were high after KD diet is not clear from the discussion. What is author's interpretation of increased CRP level after date 10.11?

Reply 4: The CRP level and WBC counts were higher and body temperature increased from October 11, but the KD began on September 28. Considering the long hospitalization and low resistance of the child, the CRP level and WBC counts were elevated due to nosocomial pathogenic infection rather than due to KD. With the decision was made to use meropenem according to the sputum culture identified the *Burkholderia cepacia* and the result of drug susceptibility test.

Changes in the text: We have modified our text as advised (see Page 6, line 95-99).

Comment 5: The author's interpretation of Meropenem's uses and CRP level rise will be helpful for the readers.

Reply 5: The child was treated with meropenem twice during the course of the disease. For the first time, the patient was treated empirically with cefodizime on admission, but he still had recurrent fever, cefodizime was changed to meropenem. Then, the infection was better controlled according to the CRP level returned to normal and no abnormalities were found in chest radiograph. For the second time, his fever recurred with the routine blood examination showed 18mg/L of CRP, $19.65 \times 10^9/L$ of WBC and 0.991ng/mL of PCT, and the sputum culture identified the *Burkholderia cepacia* meropenem was administrated on October 11 according to the drug susceptibility test and stopped On October 16 for the negative results in blood culture. Meropenem was not used again for the later anti-infection treatment.

Changes in the text: We have modified our text as advised (see Page 5-6, line 88-101).

Reviewer B

Comment 1: On line 19, the case isn't unusual for FIRES. FIRES is rare on it's own. Perhaps state that FIRES is uncommon, and then "We present the case of a previously healthy...".

Reply 1: We have made correction according to the reviewer's comments.

Changes in the text: FIRES is an uncommon disease condition. We present the case of a previous healthy...(see Page 1, line 16)

Comment 2: There are a few grammatical errors. For example, there is awkward wording in lines 23-24. Perhaps delete "was ultimately" in line 23. Line 24 is awkwardly worded.

Reply 2: We have made correction according to the reviewer's comments.

Changes in the text: Remarkably, however, the patient achieved complete neurological recovery following a ketogenic diet (KD) in the acute phases. (see Page 1-2, line 20-21)

Comment 3: On line 32, "explosive" is probably not the best word to use. Perhaps use "acute-onset, potentially fatal epileptic...".

Reply 3: We have made correction according to the reviewer's comments.

Changes in the text: Febrile infection-related epilepsy syndrome (FIRES) describes acute-onset, potentially fatal epileptic encephalopathy...(see Page 3, line 29-30)

Comment 4: Typo on line 33. "ina" should be "in".

Reply 4: We have made correction according to the reviewer's comments.

Changes in the text: ...that develops in previously healthy...(see Page 3, line 30)

Comment 5: A reference may be needed for line 35-36. "Children with FIRES develop refractory epilepsy with severe cognitive deficit 36 affecting the temporal and frontal lobe functions."

Reply 5: The relevant reference has been added into the revised manuscript.

Changes in the text: [1] Kramer U, Chi CS, Lin KL, et al. Febrile infection-related epilepsy syndrome (FIRES): pathogenesis, treatment, and outcome: a multicenter study on 77 children [J]. *Epilepsia* 2011, 52:1956-1965. (see Page 13, line 220-221)

Comment 6: Typo on line 38, "3to 15" needs a space between 3 and "to"..

Reply 6: We have made correction according to the reviewer's comments.

Changes in the text: FIRES mainly affects children 3-15 years...(see Page 3, line 35)

Comment 7: Wrong word on line 39. Shouldn't "preponderance" be "predominance"?

Reply 7: We have made correction according to the reviewer's comments.

Changes in the text: with a peak during school age and a male predominance. (see Page 3, line 35-36)

We made grammatical improvements throughout the manuscript.

Comment 8: Reference is needed for lines 45-46 about the outcome being “poor”.

Reply 8: The relevant reference has been added into the revised manuscript.

Changes in the text: [2] Van Baalen A, Hausler M, Plecko-Startinig B, et al. Febrile infection-related epilepsy syndrome without detectable autoantibodies and response to immunotherapy: a case series and discussion of epileptogenesis in FIRES [J]. *Neuropediatrics* 2012, 43 (4): 209-216. (see Page 13, line 222-224)

Comment 9: In 48, use present tense - “report” instead of “reported”. The word “the” is not needed.

Reply 9: We have made correction according to the reviewer’s comments.

Changes in the text: Herein, we report the case of a 3-year-old boy with FIRES, in whom we focused on ketogenic diet (KD) therapy in the acute phase...(see Page 4, line 53-55)

Comment 10: Line 60, is “mmol per liter” written correctly? Should it be “mmol/L”?

Reply 10: We have made correction according to the reviewer’s comments.

Changes in the text: A venous blood gas analysis showed a sodium level of 129 mmol/L, potassium 4.3 mmol/L...(see Page 4-5, line 68-69)

Comment 11: Line 87, “grand mal” is an outdated term. Replace with “Tonic clonic seizures”.

Reply 11: We have made correction according to the reviewer’s comments.

Changes in the text: the patient had frequent epileptic seizures, especially tonic-clonic seizures.(see Page 7, line 117-118)

Comment 12: Lines 115-120, can you describe outcomes of the “other treatments”?

Reply 12: We added some content description of the “other treatments” according to the reviewer’s comments.

Changes in the text:

2.2.3 Relevant symptomatic treatment

The patient was administered mannitol and glycerol fructose alternately to reduce the intracranial pressure, and the dosage and frequency were gradually reduced according to the clinical status during the treatment. The combination of dextro-ibuprofen suppository with physical cooling was effective in reducing the body temperature with recurrent fever during the course of the disease. (see Page 8, line 143-148)

Comment 13: Lines 122-127, did the patient come back for follow-up? It would be helpful to include follow-up information if available.

Reply 13: Follow-up visits were conducted 1 and 2 month after discharge.

Changes in the text: The patient continued rehabilitation after discharge from the hospital. Follow-up visits were made 1 and 2 month after discharge and the convulsions were well controlled; however, the patient was lost to follow-up 6 months after discharge. (see Page 9, line 157-159)

Comment 14: 2.3 Prognosis – the KD is not listed in prognosis and not listed as part of the discharge regimen.

Reply 14: The body temperature was stable and the seizures symptom including seizure frequency, seizure types and relief time were significantly improved after approximately 1-month of KD therapy (9.28-10.30). The further KD was administered by rehabilitation hospital and KD is not included in the discharge regimen.

Comment 15: 2.3 Prognosis – can you list any update after discharge? Has the patient returned for follow-up? I’m asking because the KD must be adhered to almost perfectly. Perfect adherence is not likely or unattainable unless the patient is unable to feed themselves and a caretaker can control the diet 100%, making sure the patient has no nourishment outside the KD.

Reply 15: Accurate dietary control was given during the PICU to ensure the KD effect, and KD was continued by rehabilitation hospital after discharge.

Changes in the text: The patient continued rehabilitation after discharge from our hospital and the KD was adhered by rehabilitation hospital. Follow-up visits were made 1 and 2 month after discharge and the convulsions were well controlled; however, the patient was lost to follow-up 6 months after discharge. (see Page 9, line 157-159)

Comment 16: Follow-up data would also be helpful, since intellectual disability is common in survivors (line 135). You mention in line 161 that the KD is useful for “long-term disease management”, and it would be helpful for you to provide patient follow-up information on seizure control and cognitive outcomes (line 162-163).

Reply 16: Follow-up visits were conducted 1 and 2 month after discharge. The patient’s convulsions were well controlled with continuing rehabilitation and KD, but unfortunately, the patient was lost to follow-up 6 months after discharge.

Comment 17: Lines 143-148 are important and should be listed earlier in the manuscript – perhaps in the literature review at the beginning.

Reply 17: We have adjusted the position of line 143-148 according to the reviewer’s comments.

Changes in the text: The most important treatment for FIRES is the control of epileptic seizures, especially during the acute phase [6]. Although general expert consensus in the literature recommends the administration of anti-epileptic drugs (AEDs) or anticonvulsants, they are ineffective in most cases of FIRES [7]. (see Page 3-4, line 45-48)

Comment 18: Paragraph on lines 165-169 seems out of place with some parts redundant. Perhaps move or disburse in earlier sections.

Reply 18: We have adjusted the position of line 165-169 according to the reviewer’s comments.

Changes in the text: However, better seizure control during the acute stage of FIRES could protect against injury to the nervous system. KD can effectively resolve super-

refractory status epilepticus (SRSE) in the acute phase and improve the prognosis of FIRES. (see Page 4, line 48-51)

Comment 19: You may not want to include “literature review” in your title, since you don’t perform a systematic literature review.

Reply 19: We have revised the title to “Ketogenic diet (KD) therapy in the acute phase of febrile infection-related epilepsy syndrome (FIRES): a case study” according to the reviewer’s comments.

Changes in the text: (see Page 1, line 1-2)

Comment 20: Perhaps revise your title to “Ketogenic diet (KD) therapy in the acute phase of Febrile infection-related epilepsy syndrome (FIRES): a case study”.

Reply 20: We have revised the title to “Ketogenic diet (KD) therapy in the acute phase of febrile infection-related epilepsy syndrome (FIRES): a case study” according to the reviewer’s comments.

Changes in the text: (see Page 1, line 1-2)

Comment 21: The “CARE Checklist” on page 12 should probably be deleted.

Reply 21: We have deleted The “CARE Checklist” on page 12.

Comment 22: Was this study reviewed by an IRB? If so, it would be helpful to include the IRB information and study number.

Reply 22: This study was reviewed by an IRB. The IRB study number is 202106057-1.

Comment 23: On line 194-195, you state the patient gave “oral and written consent for the publication of his medical data and the photographs”. Is this really the case, since he is only three years old? Please clarify the details about who gave consent.

Reply 23: We are very sorry for our negligence of this part, and the consent was given by his patients. We have made correction about who gave consent.

Changes in the text: The parents of the patient provided oral and written consent for the publication of his medical data and photographs. (see Page 12, line 217-218)

Special thanks to you for your good comments.