Author’s response to reviews

Title: Fulminant encephalopathy in a child with hyperferritinemic sepsis: a case report

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Point-by-point responses to editor

#1. Clarify novel finding of the case in Abstract and at the beginning of Discussion.

Response: Thank you very much for your professional suggestion. The novel finding of the case has been added in line 56-59, page 2-3 in Abstract which is described as below:
“Few reports have focus on MRI imaging findings on the early onset of hyperferritinemic sepsis with MODS since these children were too ill to undergo an MRI scan. However, SAE might appear before other systemic features of sepsis are obvious, and MRI could show abnormal lesion in the brain during the early course.”

The novel finding of the case has been added in line 169-172, page 6 at the beginning of Discussion which is described as below:
“MRI imaging finding on day 1 after onset of hyperferritinemic sepsis with SAE are rarely reported in pediatric patients. However, MRI could show abnormal lesion in the brain during the early course of SAE, which might contribute to appropriate management and therefore improve the prognosis of sepsis.”

#2. Initial manifestation of recurrent seizures should have been properly managed.
a) The duration of seizures is discordant: starting half a day before admission of the other hospital but transferred 6 hours after onset.
Response: Sorry for the mistake. According the medical record, the patient showed the symptoms of abdominal pain, vomiting, and seizures at 4:25 AM on January 17, 2018 and she was sent to the first hospital at 8:30 AM. We have corrected the mistake and “half a day” was substituted by “4 hours” in line 86-87, page 3-4 in revised manuscript. She was transferred to our hospital at 10:20 AM. Therefore, she was admitted to our hospital 6 hours after onset.
b) Whichever, the condition fulfills the definition of new-onset refractory status epilepticus. See Trinka et al. Epilepsia 2015 and Hirsh et al. Epilepsia 2018, etc.
Response: Yes, she fulfilled the diagnosis of refractory status epilepticus since the symptom of seizure last for hours. “recurrent seizures” had been substituted by “refractory status epilepticus” in line 86-87, page 3-4 in the Case presentation section.

#3. Add the content of the rebuttle note to Discussion.

a) Rationale of diagnosis of sepsis (Major comment 1 by Reviewer 2). It is reasonable to start treatment of sepsis as soon as possible when doubted, but other possibilities should be listed and discussed. For example, there are various non-systemic autoimmune antibodies causing encephalopathy that can be improved by immunotherapy. See Saraya et al. BMC Neurol 2019, etc.
Response: Thanks for your professional suggestion.
Rationale of diagnosis of sepsis has been added in line 179-197, page 7 in the Discussion section which is described as below:
“The blood tests showed that the WBC count, the proportion of neutrophils and PCT were very high in our patient which indicated the existence of bacterial infection. In particular, PCT was 55.77 ng/mL, which was helpful to differentiate systemic inflammatory response syndrome due to virus or autoimmune disease from bacterial sepsis. Furthermore, the amino acids and acylcarnitine results in the blood and urine organic acids excluded genetic metabolic diseases. Plasma ammonia was normal in this patient, including test for tetramines, organophosphorus pesticides, and sedatives, which were all negative in this patient. The patient did not show symptoms of skin rash or arthralgia. The antinuclear antibody spectrum was negative. There was no sign of autoimmune diseases, such as juvenile idiopathic arthritis, systemic lupus erythematosus, or vasculitis. The symptoms of this patient included fever, ferritin > 500 ng/mL, hypofibrinogenemia, and hemophagocytosis. These did not fulfill five of the eight criteria for HLH. Therefore, hyperferritinemic sepsis associated with MODS was diagnosed in our patient. We did not detect the autoimmune antibodies associated autoimmune encephalitis in this patient since she showed obvious symptoms of fulminant sepsis with MODS without outstanding symptoms of behavior, psychosis, or memory impairment. Additionally, the hyperferritinemia and high levels of PCT are rare in patients with autoimmune encephalitis.”

b) MRI findings (Major comment 2 by Reviewer 2 and Comment 1 by Reviewer 1). Comparison to previous literature and utility of ADC are worth publishing
Response: Thank you for your professional suggestion. We reorganized the part of neuroimaging in the Discussion.
Comparison of MRI findings to previous literature has been added in line 199-202, page 7 in the section of Discussion which is described as below:
“In this study, we collected data from 18 available cases of SAE (including 3 pediatric cases and 15 adult cases) in the literature, and the MRI features and prognoses are shown in Table 2.”
Utility of ADC has been added in line 212-219, page 8 in the Discussion section which is described as below:
“Fortunately, MRI was performed during the early course of SAE in our case, which contributed to a favorable prognosis. However, apparent diffusion coefficient (ADC) mapping, which can mark geometric tissue characteristics such as the size and shape of the cell structure, is not performed routinely in our hospital. This is a limitation in our case. In fact, ADC mapping is very useful in the consideration of the pathogenesis of brain lesions which show a reduction in acute neurological
diseases, but elevations in acute vasogenic edema formation or chronic tissue destruction[14].”

#4. English should be edited.
Response: Thanks for your professional suggestion. English has been edited by the expert from American Journal Experts. Editing certificate was attached as the supplement.