Author’s response to reviews

Title: A case report of a teenager with severe hand, foot, and mouth disease with brainstem encephalitis caused by Enterovirus 71

Authors:

Ying-Fu Chen (chenyfpicu@163.com)

Lan Hu (kldhl629@126.com)

Feng Xu (xufeng9899@163.com)

Cheng-jun Liu (liucwd@163.com)

Jing Li (lijingwangyi@126.com)

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Author’s response to reviews:

Dear editor,

We have responded to the reviewers’ comments below and have revised the manuscript accordingly (highlighted in red). Please find the updated manuscript enclosed.

Your consideration is greatly appreciated.

Thank you and best regards,

Mr Ying-Fu Chen

Reviewer reports:

Karen C. Bloch, MD MPH (Reviewer 1): Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

The authors have written an interesting case report of a 16-year old patient with EV-71 encephalitis, notable in that this is an unusual cause of CNS infection in this age group. This case report would be improved with the addition of more information regarding clinical findings, diagnostic workup, and therapeutic interventions. Specifically:
1. What medication was given for "cold"? Was it over the counter, or prescription?

The medicines were purchased over-the-counter by the patient’s relatives for which no details were available. This information has been included in the revised manuscript.

2. Are there any photographs of the rash or oral lesions? If so, this would be a nice supplement for the text.

No photographs of the rash or oral lesions were obtained at the time of admission, as these are the typical symptoms of HFMD. However, the lesions were described in detail in the patient’s clinical record.

3. Please provide the WBC differential on the CSF

The total number of cells was 188×10⁶/L, nucleated cells 44×10⁶/L, monocytes 37×10⁶/L, multinucleated cells 7×10⁶/L. We have included this data in the revised manuscript.

4. Were the IgM levels quantified? If so, please provide these values. Is this a commercially available assay?

Yes, IgM levels were quantified at our clinical laboratory using commercially available ELISA kit (Cat No. 20143400198) from Wantai Biopharm Inc, China. The CSF tested positive for IgM antibody to EV71, but negative for IgM antibodies against Enterovirus, herpes simplex virus, Coxsackievirus B, and measles virus. We have Chinese clinical report.

5. Please provide information on the RT-PCR—is it a commercially available assay? What gene or sequence is amplified, and is this specific to EV-71?

Yes, this commercially available RT-PCR kit (Cat No. 20133400621) from SANSURE Biotech Inc, China is designed for rapid identification of EV-71 infection during an epidemic of hand, foot and mouth disease. It is specific to EV-71 and the test was performed at the clinical laboratory in our hospital.

6. Why was RT-PCR performed only on stool and not on CSF?

The Chinese National Center for Disease Control and the guidelines for the prevention and control of Hand, Foot and Mouth Disease in China recommend RT-PCR method for detection of virus in stool and oropharyngeal secretions due to the high positive rate. The detection of EV71 in stool samples by RT-PCR is also widely used in clinical settings to monitor the development of HFMD. In our study, CSF and serum samples were used to test the IgM antibody against EV71, while RT-PCR was performed on stool only.
7. The description of the EEG report is not clear—what does "Under a coma" mean in this context? Perhaps including the interpretation of the EEG would be more helpful.

The patient was administered 5 mg midazolam twice daily on days 1 and 2 after admission to prevent agitation. He was unconscious and comatose while performing EEG on day 3. The results were indicative of diffuse encephalopathy with mixed delta and theta wave activity in the range of 1–4 Hz, which indicated abnormal brain function.

8. Why do the authors refer to this as "brain-stem" encephalitis when the CT and MRI were both without focal abnormality?

The patient had hemiplegia, bilateral pupil asymmetry (4 mm on the left side and 3 mm on the right side), shallow breathing, and sluggish papillary light reflex. Based on the above clinical symptoms, specialists in the Department of Neurology and the Department of Infectious diseases established a diagnosis of brain stem encephalitis, although the CT and MRI showed no abnormality at that moment.

9. In the discussion, the authors specify that therapy resulted in "rapid improvement". It would be useful to discuss the specific indications and literature supporting the agents that they believe benefited this child.

The patient gained consciousness and limb muscle strength recovered in about one week. However, the recovery may take several weeks to months in infants and young children infected by EV71. Thus, for the same medication and treatment received, this patient showed rapid improvement in neurological symptoms and signs.

Reviewer 2 (Reviewer 2): "PEER REVIEWER COMMENTS: To view the full report from the academic peer reviewer, please see the attached file.

REVIEWER COMMENTS FROM REPORT: The Authors report a case of complicated hand, foot and mouth disease (HFMD) in a 16-year-old male, concurrent with the detection of enterovirous 71 (EV71) in the patient's CSF, serum and feces. Progression of deficits, culminating in neurologic compromise, led the Authors to implicate EV71 as the cause of HFMD with severe neurologic compromise.

Overall impression: The case is well-written and interesting with the potential to inform clinical practice in a meaningful way.

What have the Authors done well: The Authors have done a good job of highlighting the unique / rare aspects of this case, and the importance of considering EV71 in the differential diagnosis of older children / adults presenting with HFMD and neurologic compromise in the future.
In what ways does it not meet best practice: As the Author's articulate, symptomatic EV71 infection is extremely rare in older adolescents and teenagers. However, alternate explanations for EV71 detection and/or the clinical presentation have not (yet) been sufficiently explored or communicated ("Execution" issue--see grading below).

REQUESTED REVISIONS:

Execution:

It is important to clarify the rate of asymptomatic infection in this age-group.

Thank the reviewer for the suggestion. Unfortunately, the data on the rate of asymptomatic infection in this age-group is not available.

Additionally, the Authors must stipulate what other etiologies were considered in this patient (e.g., HSV, West Nile, VZV, EBV?). This information is critical to support the assertion that EV71 may associate with HFMD in teenagers with potentially severe neurologic involvement.

Other viruses were also examined in the CSF and stool specimens of the patient. ELISA results showed negative for IgM antibodies against Enterovirus, Herpes simplex virus, Cossack virus, and measles virus in CSF, and RT-PCR results were negative for Coxsackievirus A16 in stool.

Interpretation:

The current statement that "EV71 infection may cause HFMD…” is too strong a statement for the level of evidence (single case) presented.

The sentence has been appropriately modified in the revised manuscript.

Provided that the reader can be sufficiently convinced that other reasonable entities were excluded, this report will advance the care patients with HFMD with neurologic sequelae, informing diagnostic evaluation and treatment.

Thanks for the comment. Our patient tested negative for other viruses, and EV71 was the only causative agent of HFMD that tested positive.

ADDITIONAL REQUESTS/SUGGESTIONS:

I offer the following specific comments to improve the utility and clarity of this case report.

Case Description:
Reference to "some medicines for cold" is vague and non-informative. Please state the medicines that were provided to the patient prior to admission.

The patient’s relatives were unable to provide details of the medicines used prior to admission. These were purchased from a pharmacy without a prescription.

If photographs of lesions were obtained at the time of admission these should be included as an informative figure.

We did not take photos of the rash or oral lesions at the time of admission, as these are the typical symptoms of HFMD. However, we described the lesions in detail in the patient’s clinical record.

A more thorough description of neurological examination findings is required to ensure that readers fully appreciate the deficits. In addition, please specify the pattern of left-sided facial paralysis (upper and lower face? Upper only?). Note—due to the location of the facial nerve nucleus within the brainstem (very near to the abducens nerve nucleus), and the close proximity of the nerve root to other cranial nerves, it is highly unlikely that unilateral facial nerve palsy would be the only sequelae of brainstem encephalitis. Isolated facial nerve palsy would be more typical of distal CNVII compromise (i.e., "Bell's palsy").

Many thanks for the reviewer’s comments. The patient showed left-sided facial paralysis that affected both upper and lower face. Combined with other clinical symptoms, specialists in the Department of Neurology and the Department of Infectious Diseases established a diagnosis of brain stem encephalitis with high possibility.

Was the patient chemically- / medically-sedated at the time of the EEG?

The patient was injected 5 mg midazolam twice daily on days 1 and 2 after admission to prevent agitation. He was unconscious and comatose during EEG examination performed on day 3.

Please include further details concerning "anisocoria". Were both pupils unresponsive to light?

Yes, both pupils showed sluggish papillary right reflex.

Dates of admission and testing are irrelevant to the reader. Please reference all testing to admission (i.e., CT brain was completed 5 days following admission), or symptom onset (i.e., CT brain was completed 8 days following symptom onset).

We have made appropriate revisions in this regard and have highlighted all changes.
- Findings should be reported in the order that they were received / discovered. It is unlikely that EV71 results returned on day one of admission (prior to patient decline).

We have revised the manuscript in this respect. Yes, the EV71 results returned on day one of admission.

- This patient's presentation is very concerning for HSV encephalitis. Was empiric acyclovir provided?

No. As the patient tested negative for HSV IgM, and neither head CT nor MRI findings were consistent with HSV encephalitis, acyclovir was not prescribed.

- The term "paroxysmal hypertonia" is unfamiliar to me. Please describe in greater detail. Are you implying dystonia? Posturing?

Thanks for pointing out the improper use of the word. We mean paroxysmal increase in muscle tension in limbs. Necessary changes in this respect have been made in the revised manuscript.

Discussion

- Symptoms and signs supporting the diagnosis of "brainstem encephalitis" should be explicitly stated in paragraph 2.

We have included the relevant information in the revised manuscript.