Reviewer’s report

**Title:** Clinical characteristics of enteroviral meningitis without pleocytosis in children: A retrospective single center observational study in the Republic of Korea

**Version:** 0  **Date:** 17 Jul 2019

**Reviewer:** Shane George

**Reviewer's report:**

**General Comments:**
The authors present a retrospective audit of presentations of children diagnosed with enterovirus meningitis over a 2 year period. The purpose of the review was to identify subgroups of patients who may have EV meningitis without pleocytosis based on history and examination findings along with laboratory results.

I have some concerns about the data presented and subsequent analysis and would recommend further expert analysis/review. I expect that non-normally distributed data is presented, but only means and SD are given. There are some significant confounders within the data presented which are not immediately obvious in the current format the data is presented. See specific comments below.

There is numerous references to test results determining disposition. This should rarely be the deciding factor and especially in this case of a condition which almost universally resolves without medical intervention and requires only supportive care and symptomatic management.

Overall an interesting paper which, with some significant revisions and acknowledgment of limitations, would add to the existing knowledge on the topic.

**Specific Comments:**
Abstract:
- the background statement does not truely reflect the intent of the paper, the intent of the paper appears to be to identify patient factors and clinical signs or symptoms that may indicate EV meningitis where CSF pleocytosis is not present.
- "56 of 164 (20.6%)" calculation error (=34.1%), please clarify data
- "CSF apleocysosis was significantly common in younger age groups (p <0.05)" - this sentence does not make sense. Which groups were compared, state exact p-value, limited validity if comparing to very small groups.
- "the frequency of not having pleocytosis was higher than the frequency of having pleocytosis during peak EV meningitis months" - not sure there is ever a true EV "epidemic", this sentence in clumsy and unclear, would be better reported as proportions if that is the intent. I presume the authors are reporting that the proportion of patients with EV and no pleocytosis is higher during peak prevalence periods?? Is this across all age groups or is it confounded by higher numbers of younger infants presenting?
- epidemic is again used in the conclusion

Background:
- Lines 50-61: Viral meningitis is often a clinical diagnosis, and the CSF cell counts are used as an adjunct to diagnosis. I would argue that a RT-PCR result is not required to make the diagnosis, and that particular pathogen is largely not important (with a few notable exceptions e.g. HSV) as management is based on symptom relief.
- Line 56-7: I would argue that meningitis is a clinical diagnosis, and that patients would not be discharged based on a CSF cell count alone. This contradicts line 48 which states they need opiate analgesia.
- Line 60-61: Again a test result should not determine admission or discharge, detailed assessment of the patient and their symptoms/required management should.

Methods:
Line 85: RT-PCR is available for many viruses, please clarify this.
Line 92: "The traumatic" replace with "A traumatic"
Line 93: "is defined that" replace with "was defined as a"
Line 94: specify correction used rather than referencing to a paper.
Line 106: "spinal tapping" use lumbar puncture for consistency
Line 107-108: Clumsy sentence, needs revision. Define "meningeal irritation sign"
line 113: P should by p

Results:
- report actual p-values not just < 0.05
- small sample size in ages between 3months and 3 years limit the interpretation of these data, consider combining 3m-3y into one group
- line 149-152: was this confounded by the age of patients presenting

Table 1:
- all data presented as mean/SD were they all normally distributed?
- I expect that age in particular is not normally distributed
- cell counts should be reported in whole numbers
- inconsistency in decimal places in values and ranges
- was the presence of meningeal irritation documented for all cases? I would be surprised if this was the case for all patients. especially the very young.

Table 2:
- again age presented as mean/SD, doubtful data is normally distributed
- confirm validity of comparison if non-normally distributed data
- headache comparison confounded by age (unable to assess in younger children)

Table 3:
- cell counts in whole numbers
- check for normal distributions to present mean/SD
- would appear CSF protein and CSF/Serum glucose ratios are not normally distributed given p-values of essentially identical mean/SD data presented for both groups

Table 4:
- validity of comparison to small groups 3m-3y questionable. Could consider combining these groups,
but still small sample

Figure 1:
- would be better in a table

Figure 2:
- limited value without age breakdown to help interpretation
- could be included in table with data from figure 1

Discussion:
line 162 - are there any multicentre studies? I have not had a chance to search
line 180 - "also might" replace with "may also". Also should reference source for this conjecture or explain scientific rationale
line 185-6 - you are unable to make this definite statement from the data presented, you may state the association but this does not prove causation
Line 188 - "they can easily access to" replace with "they can easily access an"
Line 188-190: clumsy sentence, need to reference source data if making this statement.
Line 196-200: this would be well explained by describing the data as not normally distributed, as expected by the data presented
line 205-213: need to describe ages of presentations during the peak season, avoid epidemic it is just seasonal variation
Line 211-213: Diagnosis of EV is not the primary consideration for performing LP in this age group, rather it is to exclude bacterial meningitis and thus guide length if antibiotic treatment
Line 214-221: Test results should not determine disposition, not all patients with viral meningitis of any sort need admission, if the cell differential support viral aetiogy (i.e. predominance of mono-nuclear cells), the patient does not require admission if symptoms are well controlled with treatments that can be given at home and there are no risk factors of more serious viral aetiologies (e.g. HSV). The exact viral pathogen is rarely a factor in the disposition decision outside of HSV encephalitis/meningitis. What was the outcome of those that re-presented? Did the RT-PCR result modify their treatment?

Conclusion:
- see previous comments about confounders to these statements
- while i don't disagree that RT-PCR gives more information, I am not convinced it changes management or outcomes

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess
Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

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