Author's response to reviews

Title: Paediatric Investigators Collaborative Network on Infections in Canada (PICNIC) Study of Aseptic Meningitis

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Author’s response to reviews:

Biomed Central Editorial
Re: MS: 5053960328307191 - Paediatric Investigators Collaborative Network on Infections in Canada (PICNIC) Study of Aseptic Meningitis

Thank you for your correspondence of 31 Jan 2006 in which you provided recommendations for revision of our manuscript. We appreciate the thoughtful comments of the reviewers and have revised the manuscript accordingly. Following is a point-by-point response to these comments:

Reviewer Martha Lepow

This is a retrospective, multicenter study with different laboratory capabilities for viral cultures and nucleic acid determinations. You may be too inclusive. The data are 8 years old and technology for diagnosis have changed with nucleic acid determinations being the standard in the U.S.

1. You should consider narrowing the inclusion to only those who had abnormal number of cells in the cerebrospinal fluid with a clinical presentation characteristic of enteroviral disease.

Response:
We agree that the data are 6 to 8 years old and the technology for diagnosis has changed. However, most communities outside major teaching centers still rely on the traditional methods of making clinical diagnoses and do not have access to real-time polymerase chain reaction (PCR) for laboratory confirmation. Since CSF pleocytosis occurs as a response to microbial pathogens in the CSF and therefore may not be marked early in disease we do not wish to exclude those children who had low white cell counts as this would bias the sample. We also believe that our current definitions are consistent with those used by others in the literature and we are reluctant to make changes that would make it difficult to compare with prior studies.

2. Once done, make a table by institution and age of subject with abnormal CSF.

Response:
We have now made a table with the ages of the subjects at the different institutions (new Table 1). As explained above, we chose not to omit the subjects with normal CSF parameters in order to be consistent with previous studies and since it is known that absence of CSF pleocytosis can occur in laboratory-confirmed infection.

3. Your "normal" cell count is much too high. At best infants < 28d may have as many as 30 WBC in the CSF - mainly lymphocytes or mononuclear cells. Any polymorphonuclear leukocytes in the CSF are abnormal. Over 28d, the white cell count should be less than 4 per cum/m. We suggest a table according to
age of subject, CSF cell counts and % PMN. With many enteroviruses, polymorphonuclear leukocytes will be more common in day 1 or 2 than later in the illness.

Response:
We have chosen the values we used based on definitions used in previous studies (reference 5 in the manuscript). In our discussion, we note that our normal values in infants <28 days may be too high but were chosen to be consistent with previous studies. However, even if a threshold of 5 WBC had been used in all age groups, 6% of infants with proven enteroviral meningitis would have had a normal CSF WBC.

We considered including a table with the different ages and CSF cell counts, but it becomes difficult to interpret in the face of bloody taps. However, we can provide such a table if the referee thinks it would strengthen the manuscript.

4. At this point you can look at the group of 233 proven enteroviral meningitis by either viral isolation from stool, throat, CSF or PCR from CSF source according to center. Do other centers’ data correlate with those from Alberta who had 52% of the patients? There are seasonal variations, but epidemics occur due to one type of enterovirus and findings may be skewed because of different viruses may have different manifestations. Also different viruses may have circulated during the 2nd year of a study.

Response:
The new Table 1 now shows the viruses isolated from the proven enteroviral meningitis cases by center and the age range of children entered in the study from each center. As predicted by the referee, there was some variation in the viruses isolated and the age of the patients between Year 1 and Year 2.

5. The virus types are interesting. Were Alberta types different from the others?

Response:
See response to #4 above.

6. Omit any patients with underlying CNS disease (37) unless they are already excluded. Now you are ready to see whether you can combine the patients with positive viral studies with those with clinical aseptic meningitis. If so then the "other manifestations" can be looked at including CSF protein and sugar, fever, etc.

Response:
We agree it is debatable whether the proven enteroviral meningitis cases should be combined with the clinical aseptic meningitis cases when reviewing clinical presentation. However, we chose to combine the two groups as our primary objective was to describe the clinical features of children with aseptic meningitis rather than only those with enteroviral meningitis. Since the clinical features we looked at were objective (fever, vomiting), we did not think the small number of patients with underlying neurologic disease would skew the results.

7. The age group of < 1 month should be looked at again as a group, especially those with low or absent cell counts and positive nucleic acid tests. Other have described similar findings, usually with absent cells in the CSF.

Response:
We agree that the infants < 30 days of age are a unique group, so have now separated out their clinical features in Figure 2 and clarified the fact that none of them presented with enteroviral sepsis syndrome. We specifically comment on the CSF parameters in this age group and have clarified in the neuroimaging table (new Table 2) and in the section about ICU admission as to which data applies to infants < 30 days of age.

8. Length of stay - only 2 days is unusual. What were criteria for discharge?

Response:
Discharge criteria were not uniform across the 8 hospital sites. However, in general in Canada once there is laboratory confirmation that the clinical meningitis syndrome is not due to bacterial meningitis, there is no suspicion of herpetic CNS disease, the child is improving and that parents/guardians are able to care for the child in the home, children are discharged with ambulatory follow-up. This typically occurs after a brief admission. In fact the 129 outpatients mentioned in the study were discharged from the Emergency Department (generally as they presented in the midst of an outbreak of aseptic meningitis and had classic clinical and laboratory findings). We can expand upon this point in the discussion if the referee thinks it would be helpful.
9. Table with demographics is too detailed and data are covered in the text and exclude the figure.

Response:
The only table in the original version of the manuscript was the neuroimaging table. We agree the footnotes are very detailed, but otherwise the reader is left unable to judge the significance of the abnormal findings. The footnotes clarify that most of the abnormal findings were likely unrelated to meningitis. We would be happy to have the table included as an appendix rather than in the body of the manuscript if the referee thinks that would be more appropriate.

We feel that the figures contain information that significantly adds to the clarity of the manuscript so deleted some of the text describing the clinical features rather than deleting one or both figures.

10. Discussion - Shorten it. The neonatal comparisons are important. Today PCR is the standard for diagnosis. One of the weaknesses of your study was varying capabilities of the different centers and different results. Most other studies reported today in the literature will have positive RNA PCR as the major criteria. Bibliography should include only those published in the last 10 years with PCR because viral isolation from CSF has been poor, it is virus dependent, whereas PCR is specific for all RNA enteroviruses.

Response:
We have shortened the discussion. The references have been revised to include only those published since 1995 as suggested. Other reviewer comments summarize previously stated issues, which have been addressed above.

Reviewer: Marvin Harper

General:
This is a straightforward study with a couple of basic aims. To describe the epidemiology of aseptic meningitis in Canada including the seasonality and etiologies. Secondly there is an attempt to describe disease by classification into subcategories and the use imaging.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. Is it meningitis without pleocytosis? It is interesting that one third of infants with EV had no pleocytosis. But what does it mean? I am not even certain why the test would have been sent. I tend to agree with the authors that the problem is likely in the definition of what is normal CSF for the infant. It might be worthwhile to apply a single standard of >7 wbc (or 8) across all age groups.

Response:
We believe that early in the course of bacterial or viral meningitis, there can be organisms in the CSF with no or minimal pleocytosis - especially in the young infant where the inflammatory response can be delayed or dampened. Absence of pleocytosis occurred in about 6% of the proven enteroviral cases in this study. As explained to the other reviewer, we prefer to use the CSF WBC parameters used in previous similar studies for consistency and to account for the fact that the normal range is clearly higher in the first month of life.

2. The very low rate of sequelae is interesting but was any systematic follow-up testing done? If not, this should be listed as a limitation.

Response:
We now clarify that long-term follow-up did not occur.

3. It is quite surprising that such a high proportion of children had diagnostic imaging of the head and even more surprising that 27% were abnormal. The precise nature of these abnormalities were unclear to me. It would be more useful to report the proportion with an abnormality of the CNS thought to be somehow related to the infection (excluding pre-existing abnormalities or sinusitis). Table 1 is not that useful and the overall presentation of this data could be incorporated into the text and likely improve clarity.
We agree that the rate of neuroimaging was higher than one would have predicted. This could relate to the ready availability of neuroimaging in the Canadian health care system and the anxiety generated in health care providers by young children with neurologic disease. The abnormalities are described in the footnotes of Table 2 (previous Table 1). As mentioned to the other reviewer, it would be acceptable to us to have this table as part of the Appendix rather than the main body of the manuscript, but think the details would be of interest to some readers. Unfortunately, in the vast majority of cases, the relationship between the abnormalities and meningitis is not established by a radiologist or neurologist, so we think it would be inaccurate for us to try to establish that relationship. Therefore we leave it up to the reader to interpret the findings. However, we do comment that only 3 patients had abnormalities that would possibly require intervention (all had hydrocephalus).

Thank-you for reviewing this revised version of the manuscript. We would be pleased to consider any other suggested revisions.

Joan L. Robinson