Reviewer's report

Title: Young male patients are at elevated risk of developing serious central nervous system complications during acute Puumala hantavirus infection

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Reviewer: Clas Ahlm

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The manuscript “Young male patients are at elevated risk of developing serious central nervous system complications during acute Puumala hantavirus infection” by Hautala et al. describes CNS complications in patients with hemorrhagic fever with renal syndrome caused by Puumala hantavirus in Finland. Part of the patient population has been presented previously (Hautala et al. 2010, reference 7).

Puumala hantavirus infection is rather common in Northern and Central Europe and the findings of CNS involvement merits increased attention. The observation that young male patients are at elevated risk is interesting but there is no explanation or discussion about the possible reasons for this.

Major Compulsory Revisions

The authors state that an additional aim for the study was to “analyze the clinical findings in order to search for an explanation for the CNS involvement”. This part is not analyzed enough and additional results could be provided or tests performed.

An important and interesting issue is if the severe CNS complications were caused by viral infection of the brain per se (meningoencephalitis /encephalitis), a vascular thrombosis and infarction, hemorrhage or a vasculitis. Puumala viral RNA has been detected and presence of specific IgM in CSF supports that Puumala virus indeed may cause CNS infection. However, how Puumala virus may cause the different clinical manifestations is still not obvious. Most patients had pituitary hemorrhage in their MRI, what may be the cause for this finding?

Was there a damage of the blood-brain barrier detected by an abnormal CSF/serum albumin index? The body weight was used as measurement of “increased tissue permeability”. Do the authors mean increased permeability in general or could there be specific blood - brain barrier damage?

Was any patient examined by CT-angio?

There are several markers that could be used to detect inflammation and tissue damage in viral CNS infections, e.g. neopterin, S-100B, cytokines, metalloproteinases etc.

Are there any CSF left for further analyses this would strengthen the manuscript. Body weight and serum creatinine levels are crude and not appropriate measurements alone to explain the CNS complications.
Minor Essential Revisions

Introduction, page 3, 2nd paragraph, line 4. It would be preferable that the authors provided the original studies regarding the different CNS manifestations instead of the reference 1 which is a review.

Material section. It should be stated whether the 8 patients with major CNS complications were from the same hospital and during which period they were collected.

How long was the follow-up of the patients?

Describe more of the technical details about the MRI examination. Was it both T1 and T2 weighted, and were contrast used?

Was Puumala specific IgG and IgM in CSF analyzed in the same way as sera, i.e. by Reagena or IFA? It could be described in detail since this is a crucial method in this study.

Results. Page 9, line 5-7. The word “control phase” could be changed to control examination.

The mean differences in length of the vitreous cavity between acute phase and the control examination were calculated but were these differences statistically significant? In this sentence there is an extra “the” that could be omitted.

Discussion. The authors could discuss more in depth the possible pathogeneses in CNS complication due to Puumala virus infection and why young male patients seems to be at elevated risk. What is known about age and sex differences in other viral CNS infections?

Discretionary Revisions

In legends to Table 1, I believe that the sentence “In addition, their….p<0001” could be moved to a footnote instead.

Discussion. 4:th paragraph, line 3 “exhiting” should be “exhibiting”.

Last sentence, a “to” should be inserted “leading … injury…..”

4:th paragraph. The sentence “Our previous study… affected (7). Could be misunderstood and needs to be rephrased.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.