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: Jukka Mustonen

Reviewer's report:

There are some important messages in the paper. NE may cause severe central nervous system (CNS) complications that possibly are related to the age and sex of the patients, some patients develop permanent neurological impairments and pituitary insufficiency after PUUV infection may be more common than previously believed.

Major compulsory revisions

How were the 40 patients selected from those NE patients that were treated in the Oulu University Hospital during September 2005 to February 2008? How many patients were treated at the hospital during this period? In the previous paper (Hautala et al. 2010) there were 58 patients. Is it possible that the selection of the patients might have an influence on the results?

The authors have used several definitions to describe CNS manifestations of the patients: CNS symptoms, CNS involvement, CNS complications, CNS-related symptoms, CNS injury, CNS-related findings, CNS findings, CNS involvement and CNS illness. It is difficult to understand, for instance, what is meant by saying “We compared the clinical properties of NE patients who suffered CNS symptoms to those without CNS involvement” (Introduction, last paragraph). Terms used should be clearly defined. Especially as practically all patients had “symptoms suggestive of CNS involvement” (Results, first paragraph).

What hormonal analyses have been performed in the patients to find out hormonal deficiencies?

Was there any relation between CSF PUUV IgM positivity/negativity and the time from beginning of the clinical symptoms of NE to that when the CSF specimens were obtained?

Results (Kidney failure and tissue edema). It is quite obvious that high plasma creatinine levels, high weight change and low urine output correlate with each others because all of them reflect the severity of acute nephritis of NE. What are here the “CNS-related findings” mentioned in the last sentence of this paragraph? (see above).

Discussion, second paragraph. What do the authors want to say in the first sentence? Also the speculation presented here is difficult to understand. Express
more clearly, please.

Discussion, fourth paragraph. The authors should discuss more why NE causes severe CNS complications in young males. What might be the pathogenic mechanisms? As noted in the text, serious complications have rarely been reported in children. There are also some data in the literature that females might have more serious hantavirus caused disease than males.

Minor essential revisions

Table 1. It is not clear in the table text between which groups the statistical comparisons presented have been performed?

Table 3. Is “encephalitis” really a MRI finding?

**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.