Reviewer's report

Title: Encephalitis temporally associated with Japanese encephalitis vaccine: Case report

Version: 3 Date: 10 February 2011

Reviewer: Susan Hills

Reviewer's report:

• Major Compulsory Revisions

General comments
1. This report contains some interesting and useful information. However, the authors need to more clearly interpret and present their findings. They report four cases of laboratory-confirmed Japanese encephalitis (JE) neurological infection that occurred in temporal association with vaccination with live, attenuated JE vaccine. Patients were vaccinated 7-14 days prior to illness onset. It is certainly feasible the events were due to JE vaccination. However, all cases occurred during the JE virus transmission season in a JE-endemic area of China with relatively high JE incidence. The incubation period for JE is 5-15 days. Therefore these events could equally be a result of natural infection with JE virus (JEV). JE vaccination is very unlikely to prevent a wild-type infection acquired around the same time as vaccination was given. A third possibility, although less likely, is a traumatic tap when lumbar puncture was conducted, with neurological infection due to another etiology. Anti-JEV IgM would be expected in the serum of patients vaccinated with live, attenuated JE vaccine, and indeed was detected in two of the patients tested. In the case of a traumatic lumbar puncture, the anti-JEV IgM detected may have been from blood contamination of CSF. The discussion section of the paper needs to clearly outline these different possibilities for the reader who may not be as familiar with JE infection as the authors are. Currently, the discussion section assumes the cases were adverse events and begins by comparing results to other occurrences of adverse events after vaccination. Instead, an interpretation of the events needs to begin the discussion section.

2. I also have some epidemiological and scientific concerns that could be alleviated by adding additional clarifying data to the paper. Until now, there have been no other reported cases of neurological adverse events despite the live, attenuated SA 14-14-2 vaccine being used in several hundred million children over a period of 20 years. The authors report here four cases of neurological disease following vaccination occurring over a period of three months in two districts. Epidemiologically, this is an extremely unusual event. Did this trigger an in-depth investigation? Were the batch numbers of the vaccine used the same in all four cases? If so, was vaccine with the same batch number used in other parts of China at the same time and were there similar adverse events reported? If not, why were the cases only reported in these two districts? Were these cases
reported to the manufacturer and was there any neurovirulence testing conducted? Were the patients' laboratory tests repeated and confirmatory testing done? Additional data or some discussion and explanation of the above issues will be very important for readers to understand this paper.

Specific comments

Abstract

3. Third paragraph: The comments in my first paragraph (above) need to be reviewed and consideration given to revising the conclusions accordingly. In addition, not only surveillance of adverse events, but full investigation of any events that occur should be recommended (irrespective of the time of year).

Background

4. Second paragraph: more complete information on available safety data for SA 14-14-2 vaccine should be included, as only one of many available studies is referenced.

5. Third paragraph, third sentence: Can you provide a reference for the performance of the ELISA used for diagnosis? It would be useful to know its sensitivity and specificity?

6. Third paragraph, seventh sentence: This is the first time the word “study” is used. Was this a study on JEV infection, encephalitis, adverse events after vaccination or another type of study? What was the study methodology?

Case presentations

7. First paragraph, eighteenth sentence: The word “about” is used in the phrase “she had received the JE vaccine about two weeks prior…”. The dates of vaccine receipt and onset of illness are critical pieces of information for this report. Please supply the exact date the vaccine was given, or explain why this information is not available.

8. Is there information on whether the cases had had previous doses of JE vaccine? Three of the cases were 4 or 5 years of age and may have had prior doses?

9. A gram stain was done on Case 1. Was other testing conducted on this patient or the other three patients to investigate other etiologies?

Discussion

10. First section of the discussion should be rewritten to interpret and explain the findings to readers (see first paragraph in my review).

11. First paragraph: The authors have described and referenced only one other encephalitis case after JE vaccine (inactivated vaccine). It is not clear why they chose this case and did not include reference to other literature on neurological events after JE vaccine? This paragraph includes information on adverse events following some different types of vaccines, but the main message is unclear? It would be helpful for the paragraph to be rewritten clearly stating the main messages and conclusions.
12. First paragraph: The sentence “Further studies should therefore be performed in an attempt to isolate virus or viral products” is unclear – virus isolation and PCR was attempted. What other studies would the authors consider?

13. Second paragraph, second sentence: “Although no seizures were witnessed at admission” does not seem to concur with the case descriptions; in two cases “prolonged convulsions” during hospital admission were noted.

14. Second paragraph, third sentence: it is not clear how the recommendation is derived which says that pediatricians should be aware that encephalopathic children recently vaccinated with JE vaccine may deteriorate rapidly. From the case descriptions, only two of four children (50%) deteriorated rapidly. In addition, the cases were not confirmed to be encephalopathic due to vaccination. There seems to be insufficient data on which to base this recommendation?

Conclusion

15. The authors conclude that “surveillance is needed before, during and after the JE epidemic season in endemic areas to provide comprehensive data regarding the potential link between the vaccine virus and illness”. A more complete public health message may be emphasizing that continued good quality surveillance for adverse events is important (irrespective of JE season), as well as careful and thorough investigation of any events that occur.

• Minor Essential Revisions

Title

16. Should be “Four cases reports” not “case report”

Abstract

17. In the first sentence of “case presentations”, consider the wording “detected in JE-endemic areas during the JE virus transmission season”.

Background

18. First paragraph, first sentence: “a” major cause rather than “the” major cause (or define where it is “the” major cause).

19. Second paragraph, last sentence: the infections were associated with vaccination (not the patients).

20. Third paragraph, first sentence: JE-endemic (not epidemic)

21. It would be helpful to note when the JEV transmission season occurs in the area where the study was conducted.

Case presentations

22. First paragraph, fifth sentence: unclear what “physical examination revealed…prolonged convulsion” means? Was the patient in status epilepticus?

23. First paragraph, tenth sentence: unclear what “he revealed symptoms of …and then presented with confusion and prolonged convulsion” means?
24. First paragraph, sixteenth sentence: “her consciousness reduced to lethargy” is unclear; lethargy is not a state of consciousness.

25. First paragraph, eighteenth sentence: “she then developed altered sensorium” is unclear, because in the sixteenth sentence it says she had become drowsy. At the end of the sentence, consider “finally became unconscious”.

26. Second paragraph, seventh sentence: The word “unfortunately” should be removed (no virus or product was detected, likely because it had been cleared).

Discussion

27. Second paragraph, third sentence: “pediatricians” not “pediatrics”; “pediatric patients” not “children patients”.

Discretionary Revisions

To give context to the study, it would be helpful to include the population size and number of JE vaccine doses given in the study area.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Not suitable for publication unless extensively edited

**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.