Reviewer's report

Title: Antibodies against gonadotropin-releasing hormone (GnRH) and destruction of enteric neurons in 3 patients suffering from gastrointestinal dysfunction

Version: 1 Date: 14 October 2009

Reviewer: Willemijntje Hoogerwerf

Reviewer's report:

Major

Case presentation 1 is a little confusing. The patient is described to have a longstanding history of nausea, vomiting and severe abdominal pain in association with weight loss. However, he is labeled as having IBS based on ROME II criteria. This patient does not appear to have IBS. His clinical presentation as well as his gastric emptying scan are most consistent with gastroparesis. The authors even describe the small the intestine as macroscopically normal and with normal peristalsis. At this point I would have expected that they would have obtained a gastric biopsy but they go on to describe that the small intestine was biopsied and that histopathology suggested ganglioneuritis. In the end, this patient ends up being labeled as having an enteric neuropathy.

It is unclear why the biopsies were obtained from the small bowel if the clinical symptoms and the gastric emptying suggest gastroparesis. It is hard to understand the significance of the histopathological findings in a small intestine that apparently demonstrated normal peristalsis. The biopsies should have focused on the stomach.

Case 2 may have represented a case of IBS although reflux esophagitis with secondary dysmotility cannot be ruled out based on the limited description. Case 3 is a case of an endstage diabetic with gastroparesis who ends up dying. Clearly, this patient was severely ill with multiple medical problems and the only case with high CD40 levels. Only serum from this case altered neuronal cell survival and this could be due to a variety of unknown factors.

The rationale for looking at CD40 levels should be introduced in the introduction. No rationale is provided.

The authors stated that the number of surviving neurons was counted. However, how does that have any meaning if we do not know with how many neurons they started out with. Although the authors state that surviving neurons were compared to controls, this would only be acceptable is the same number of neurons was present in all wells at the onset of the experiment.

The authors assessed the effect of human sera on cultured rat neurons. What is
the percent homology between the human and rat GNRH. What was the hypothesis behind this experiment in which case sera (with the only common denominator the presence of GNRH antibodies) was cultured with rat neurons? The authors stated that GNRH antibodies raised in rabbit (presumably against rat?) did not alter neuronal survival. Why did they even do this experiment? The cultured data were not at all helpful and their rationale remains elusive in the current version of the manuscript.

Minor

Clarify the meaning of 4 DIV.

Figure 3 was not available on line for review.

The histopathology findings should be condensed.

1. Is the question posed by the authors well defined?
No, this study is very descriptive. Essentially, they are looking for the presence of GNRH antibodies and are trying to suggest that these may play a role in the pathogenesis of dysmotility disorders.

2. Are the methods appropriate and well described?
The methods are reasonably well described but need to be improved (see comments)

3. Are the data sound?
Overall, the data are extremely weak. The cases are quite heterogeneous. Case 1 is more consistent with a case of idiopathic gastroparesis. Case 2 is not all convincing of IBS and case 3 is a case of a patient with diabetic gastroparesis who was so severely ill that he died (thus, numerous factors may have played a role in the effect of this pts sera on neuronal survival). The number of cases is too small to make any conclusions. The authors already published a case report on this topic and this manuscript does not go much further then this. The cell culture data do not support a case for GNRH antibodies and at best, GNRH, antibodies can be added to the every growing list of markers and antibodies that may or may not play a role in the pathogenesis of dysmotility syndromes.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
Yes

5. Are the discussion and conclusions well balanced and adequately supported by the data?
No

6. Are limitations of the work clearly stated?
No
7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
Yes

8. Do the title and abstract accurately convey what has been found?
Yes but it is a potpourri of findings without a clear or comprehensive hypothesis that do not hang together tightly and that do not lead to a solid conclusion.

9. Is the writing acceptable?
Yes

**Level of interest:** An article of insufficient interest to warrant publication in a scientific/medical journal

**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'