Author's response to reviews

Title: Expanded Dengue Syndrome: Subacute Thyroiditis and Intracerebral Hemorrhage

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Author's response to reviews: see over
Dear Editor

BMC Infectious Diseases

I am writing to you on behalf of my co-authors. Authors are thankful for the comments of the referees.

Following is the point-to-point response to the concerns of the referees.

**REFEREE 1:**

*(Major Compulsory Revisions)*

**REFEREE’S COMMENT 1:**

A. Abstract:
1. While writing sentences of historical importance like “on seventh day after onset of fever, patient developed severe headaches... Patient also developed painful neck...” – maintain a proper chronology of events.

**AUTHORS’ RESPONSE:**

We have made following modification in the abstract to clarify the proper chronology of events.

“On **7th day of illness** patient became afebrile, but he developed severe headaches and unconsciousness lasting for about two hours which was followed by altered behavior. **On 9th day of illness patient** developed painful neck swelling accompanied by fever, tremors, palpitation, hoarseness of voice and odynophagia.”

**REFEREE’S COMMENT 2:**

B. Introduction:
1. Paragraph 2, sentence 2 (“Dengue is the most rapidly spreading mosquito...”): Provide a reference.
AUTHORS' RESPONSE:
The statement has been modified: “Dengue is the most rapidly spreading mosquito borne viral disease in the world”
Reference has been provided.

REFEREE'S COMMENT 3:
2. In the last line of the second paragraph the authors coin the term “dengue thyroiditis”. It is a fact that intracerebral haemorrhage, subacute thyroiditis occurred in a patient with dengue infection. That does not necessitate a cause –effect relationship. This is in its own right an association at best. The coinage is discouraged.

AUTHORS' RESPONSE:
Authors agree with the referee that a clear cause-effect relationship cannot be established.
We have modified the statement accordingly: “To the best of our knowledge, this is the first case report of subacute thyroiditis in a patient with dengue fever.”

REFEREE'S COMMENT 4:
C. Case report:
1. The mode of diagnosis of dengue should be very clearly indicated. Mention the name of the kit used and the method of ELISA for detection of IgM. Malaria, leptospira and past dengue infection often cause false positive elevations. Were they ruled out? Also, mention the titre of the positive IgM ELISA.

AUTHORS' RESPONSE:
Diagnosis of dengue was established by performing Indirect IgM ELISA using commercially available kit (Human GmbH, Wiesbaden, Germany). The titre of IgM ELISA was 1.937 (cutoff = 0.524). We have added following statement: “Anti-dengue IgM antibodies were measured by indirect IgM ELISA using commercially available kit (Human GmbH, Wiesbaden, Germany). The ELISA for indirect IgM antibody detection uses Dengue specific antigens (DEN-Ag) coated on microtiter wells. IgM titre on day 10 was 1.937 (cutoff value 0.524).”
Patient was admitted to the hospital while he had become afebrile. His blood film did not reveal malarial parasite. Patient was not tested for leptospirosis.

Patient was tested negative for anti-dengue IgG antibodies during febrile phase on screening test (lateral flow immunoassay). Following statement is added: “During febrile phase anti-dengue IgM and IgG were tested negative on screening test (lateral flow immunoassay).” Although we cannot rule out with certainty a prior dengue infection in this patient, recent febrile illness during an established large dengue outbreak and a negative initial IgM and IgG antibodies make a prior dengue infection less likely.

**Referee’s Comment 5:**
2. Paragraph 1, sentence 4 (“On 7th day of illness his fever resolved”), paragraph 2, first sentence (“On second day of hospitalization...”) and last sentence of the section (“Patient was discharged on 8th post-admission day”): It is very confusing. The chronology of symptomatic evolution is difficult to understand. Clearly mention the day of illness on which he was admitted and reframe the said sentences and the third paragraph likewise.

**Authors’ Response:**
The day of illness on which patient was hospitalized was not mentioned which made it difficult to understand the chronology of the events. Patient was hospitalized on 8th day of illness. We have made following alterations: “On 7th day of illness his fever resolved, but he developed severe headache and within few hours became unconscious. Patient regained consciousness after two hours but headache, altered behavior and loss of bladder control persisted. In this condition (i.e., 8th day of illness) he was brought to the hospital.”

**Referee’s Comment 6:**
3. Third paragraph: ESR values must be given (anti – TPO levels may be added), otherwise differentiation from transient thyrotoxic phase of Hashimoto’s thyroiditis is difficult.

**Authors’ Response:**
ESR values are added. “Erythrocyte sedimentation rate (ESR) by Westergren’s method was 62 mm in 1st hour.” Anti-TPO levels are not available.
REFEREE’S COMMENT 7:

D. Discussion:

1. Paragraph 2, sentence 4 ("A frontal lobe hemorrhage should strongly be suspected in a case of dengue fever who presents with these symptoms along with severe headache and/or loss of consciousness"): This is generalization. Any cause of rise of intracranial tension may culminate in severe headache, altered sensorium or loss of consciousness. Personality changes, more related to frontal lobe lesions, however may not be clinically apparent in a stuporous patient. This sentence should be reframed.

AUTHORS’ RESPONSE:

The sentence: “A frontal lobe hemorrhage should strongly be suspected in a case of dengue fever who presents with these symptoms along with severe headache and/or loss of consciousness.” has been replaced by following sentence: “Intracerebral hemorrhage should be suspected in patients with dengue fever who develop headache and/or change in mental status.”

REFEREE’S COMMENT 8:

E. References:

1. How is the reference no. 6 relevant? I am sure the authors can find a better and succinct reference for their intended purpose.

AUTHORS’ RESPONSE:

Reference no. 5 is a report of intracerebral hemorrhage in a patient with dengue infection. Reference number 6 is an additional reference of a case report of bleeding within a pituitary tumor in a patient with dengue infection. Second reviewer has advised to add another reference of report of two cases of pituitary apoplexy resulting from hemorrhage within pituitary tumor during dengue infection. According to these case reports, dengue may be a risk factor for hemorrhage in pituitary tumor. However, if editors agree authors have no objection removing this reference.
MINOR ESSENTIAL REVISIONS

REFEREE’S COMMENT 9:
A. Case report:
1. First sentence: 1 20 – year old should be addressed as a “man” rather than a “boy”. Same applies for the abstract section.

AUTHORS’ RESPONSE:
Agreed and changes made.

REFEREE’S COMMENT 10:
2. Anti dengue antibody tests are well known for cross reactivity with other flaviviridae. West Nile has been shown to have systemic dissemination with sites that include the thyroid. Was specific serology to other flaviviridae especially West Nile sought for?

AUTHORS’ RESPONSE:
No. In the setting of an established large dengue outbreak (PCR confirmed cases of dengue infection at the same time and location), we didn’t go for specific serology for other flaviviridae.

REFEREE’S COMMENT 11:
3. Was primary vs. secondary dengue infection ruled out?

AUTHORS’ RESPONSE:
There was no prior history of symptomatic dengue infection. A negative IgG by ICT method during the febrile phase may favor primary dengue infection. However, we did not go for definite evidence of primary versus secondary dengue infection.

DISCRETIONARY REVISIONS
REFeree’s comment 12:
Discretionary Revisions
A. Case report:
1. Is any follow–up available? Did the thyroid function normalized or was the patient rendered finally hypothyroid?

AUTHORS’ RESPONSE:
The follow-up is not available.

REFeree’s comment 12:
2. Paragraph 3, sentence 4 (“Serum AST was 117 U/L and ALT was 62 U/L”): it would be nice to know the serial changes in the liver enzymes.

AUTHORS’ RESPONSE:
We have provided levels of serum AST and ALT at admission and discharge: “Serum AST levels were 117 U/L and 67 U/L at admission and discharge respectively. Serum ALT levels were 62 U/L and 40 U/L at admission and discharge respectively.”

REFeree 2:
MINOR COMMENTS:

REFeree’s comment 1:
Minor comments:
1-) Abbreviations should be defined when first used;

AUTHORS’ RESPONSE:
We have defined abbreviations in the revised manuscript.

REFeree’s comment 2:
2-) Figure 1 should be removed;
AUTHORS’ RESPONSE:

Figure 1 is a graphical representation of changes in white cell counts and platelet counts during the course of the illness. Authors have no objection if editors decide to remove the figure 1.

REFEREE’S COMMENT 3:

3-) Recently, two cases of pituitary apoplexy secondary to dengue infection have been reported and should be referred (Wildemberg LE et al Endocr Pract. 2012 Jan 31:1-17).

AUTHORS’ RESPONSE:

We have added: “Hemorrhage within the tumor of pituitary gland resulting in pituitary apoplexy has also been reported during dengue infection.” The reference has been added as reference number 7.

Kind Regards

Muhammad Zaman Khan Assir