

Response Letter

Dear Editor

Thank you for comments.

On behalf of my co-authors, we very much appreciate the time and effort you have put into your comments on our manuscript (ID 62237).

We have carefully revised the manuscript. We have submitted a revised version of our manuscript. *All the changes are marked in bold letters. We are more than happy to make any further changes that will improve the paper.*

Thank you again for your attention and consideration.

Sincerely yours,

Dr Ashish Kumar Jha

MD, DM

Reviewer 1

Comment to Authors-

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments :

The review manuscript written by Kumar Jha et al. describes a comprehensive overview on the neurological manifestations of HEV infection, which is not well known even in gastroenterologists. Therefore, the manuscript is important for the management of HEV infection. There are some concerns that need to be addressed.

Minor points.

1. **It is unclear if there are any differences in the occurrence of neurological manifestations between other types of viral hepatitis. If so, it should be discussed on that point.**

Response

We thank the reviewer for the assessment of our article.

Neurological disorders have also been described in viral hepatitis A, B and C. Hepatitis C virus infection is often associated with neuropsychiatric disorders, including peripheral neuropathy (mainly sensory), cognitive impairment and cerebrovascular accidents.

Encephalitis, myelitis, encephalomyelitis and GBS are rarely described in patients with Hepatitis C virus infection. Hepatitis A virus infection is rarely associated with neurological disorders, especially GBS and encephalitis. Other hepatitis A related-neurological disorders include meningoencephalitis, meningitis, transverse myelitis, peripheral neuropathy, optic neuritis, neuromuscular junction and muscular disorders. Hepatitis B virus infection is rarely associated with neurological disorders, especially GBS (most frequent) and peripheral neuropathy. GBS and peripheral neuropathy have been reported with viral hepatitis A, B, C, and E. *It is interesting to note that NA is described in HEV infection alone.*

2.The prevalence of neurological manifestations is different among countries. The authors should discuss on that point.

Response

The prevalence of neurological manifestations in different geographical locations is discussed. Geographic distribution of HEV-related neurological disorders are shown in table-3.

Reviewer -2

Comments to Authors - Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: In this review article the Authors addressed Hepatitis E virus (HEV) extra-hepatic manifestations (EHM) and neurological disorders which are most common EHM associated with HEV (involving both the peripheral nervous system and central nervous system (CNS) together or in isolation). This is a very relevant clinical topic since there is a paucity of data on the HEV-related neurological manifestations; and these data are mostly described as case reports and case series. They analyzed data of 163 reported cases of HEV-related neurological disorders. The mechanisms of pathogenesis, clinico-demographic profile and outcomes of the HEV-related neurological disorders. Interestingly, nerve root and plexus disorder are most

commonly reported disease followed by meningoencephalitis. They also report associations with Central nervous system disorders, Guillain-Barré syndrome, Neuromuscular junction and Muscle disorder.

In my opinion this is a well-written review article of clinical relevance. To improve the manuscript I suggest to add data about risk factors for HEV in the 163 reported cases, complete clinical features including a table reporting the liver enzyme serum levels as well as immunoglobulin serum levels and autoantibodies (if known).

Response

Thank you for review of our manuscript.

A complete clinical feature of all 163 cases was not mentioned because of widely variable clinical findings of neurological disorders. Salient clinicodemographic features of different diseases are discussed in text and summarized in Table-3. Clinical details of most frequent diseases (NA and GBS) are further described in a new Table-4. Clinical details of rare diseases are described in the text. Complete details of all liver enzymes were not available in all studies. Instead of mentioning liver enzyme levels of each patient, we have calculated median (range) value

of liver enzyme elevation (ALT) in different neurological disorders (Table 3). Source of infection, serum immunoglobulin levels and autoantibodies are not mentioned in the majority of studies. Available information regarding the risk factors of infection and autoantibodies are described in a new Table-4.

Reviewer -3

Comments to Authors:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: well written manuscript with a nice review of neurological manifestations of HEV Needs language editing.

Response-Thanks you review of manuscript and positive comments.

Our manuscript has been reviewed and edited by a professional language editing service, so we hope it now matches the journal standard (Certificate attached)

EDITORIAL OFFICE'S COMMENTS

Thank you for giving us opportunity to revise our manuscript.

Science editor Comments

1. The questions raised by the reviewers should be answered;

Response

We have carefully revised the manuscript.

2. The authors need to provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement.

Response

Provided

3. **Language certificate**

Response:

Our manuscript has been reviewed for clarity by a professional language editing service, so we hope it now matches the journal standard (Certificate attached).

4. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Response

Provided