Author's response to reviews

Title: A case of limbic encephalitis presenting as a paraneoplastic manifestation of limited stage small cell lung cancer

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Author's response to reviews: see over
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Dear Editor,

Many thanks for asking us to revise our manuscript. Please find the response to both reviewers. We have amended the manuscript according to reviewers’ suggestions and replaced MRI images showing the medial temporal abnormalities much more clearly. Please do not hesitate to contact me if you need any further information.

Kind Regards

Ahmed Fahim
Mohammad Butt
Damian McGivern
Response Reviewer 1

We thank Dr Saidha for reviewing our case report and appreciate the invaluable comments made to improve the manuscript. Following are the responses to the points raised in the review.

Major Points:

There is insufficient evidence provided in this report to support the diagnosis of limbic encephalitis/LE. The classic triad of limbic encephalitis is short-term memory impairment, temporal lobe seizures and behavioural/psychiatric disturbances. The typical MRI abnormality associated with LE is bilateral medial temporal hyper-intensity. Apart from cognitive impairment in this case, there is no evidence to corroborate a diagnosis of LE. The MRI with arrows (Fig 5b), which apparently shows areas of high signal consistent with LE, is not adequate. Firstly it is a sagittal scan and the arrowed areas of hyper-intensity are in the frontal lobe (not the “limbic system”), with no obvious hyper-intensity in the temporal lobe. An axial FLAIR scan is probably the best way to demonstrate the bilateral medial temporal hyper-intensities typical of LE (although even an axial T2 or coronals at the level of the medial temporal lobes would suffice).

Also was an EEG performed? The patient was encephalopathic with impaired memory – which may be a manifestation of non-motor partial seizures. Even the presence of temporal epileptiform activity may have been helpful in providing some support for the presence of possible LE. Have the authors considered that perhaps the patient was simply encephalopathic on account of underlying malignancy with hyponatraemia. Could there have been any infection contributing to the encephalopathy – for example respiratory infection. It appears that there is also a right lower zone opacity on the CXR.

Response

We do agree that the MRI images provided with the initial manuscript did not show areas of hyper-intensity in temporal lobes, hence after reviewing the MRI images (Both T2 and FLAIR) we have substituted the images after discussion with our radiologist and included two axial FLAIR MRI images (Figure 5a and 5b) to demonstrate the abnormal signals from both hippocampi (more prominent on the left than right). The signal abnormalities from both hippocampi could not be seen in one axial slice, so we have to show bilateral abnormalities in two separate images. We do
agree that the previous images were showing evidence of sub-cortical ischemia rather than high signal from limbic area.

The cognitive impairment would have definitely be made worse by initial hyponatremia but it is unlikely that the degree of hyponatremia would have accounted for change in mental state and memory loss. Subsequently, serum sodium concentration did normalise without significant change in patient’s cognitive state. However, following treatment with chemotherapy, her cognitive function did improve. We believe that clinical picture of short-term memory loss/behavioural disturbance in association with bilateral medial temporal (Hippocampus) hyper-intensity on axial FLAIR MRI in association with small cell lung cancer is consistent with the diagnosis of paraneoplastic limbic encephalitis.

We agree that EEG would have supported the diagnosis of LE and could provide useful additional information. However, in the absence of history of seizures and evidence of typical MRI abnormalities in a patient with small cell lung cancer, provided us with sufficient evidence of paraneoplastic limbic encephalitis. Hence an EEG was not performed in this case.

There was no clinical evidence of infection (no symptoms of cough, sputum, urinary symptoms and she was apyrexial with normal inflammatory markers, urine dipstick and culture) at presentation so we do not think that there was enough clinical/laboratory evidence of either lower respiratory or other infection to be responsible for cognitive dysfunction. However, 3 weeks after her initial presentation, she did develop evidence of lower respiratory tract infection, and the chest radiograph initially provided was taken at that point. Hence we have included the appropriate image (chest radiograph at presentation), which does not show any opacity on right side (Figure 1).

**Minor points:**

1- Non-contrast MRI scans do not show areas of high signal uptake: Uptake refers to contrast enhancement. The nomenclature for MRI is intensity – hypo, iso or hyper.

2- No proposed mechanism for the collapse and loss of consciousness has been provided by the authors

3- Was an ABG performed? Was a full MMSE performed? Was more detailed cognitive assessment such as Rivermead behavioural memory testing performed? Why did the pt only score 7/10 in the MTS?
4- The neurological examination should include particular reference to the absence of signs suggestive of cerebellopathy/peripheral neuropathy, in the context of a presumed paraneoplastic syndrome.

5- CT head was with contrast (should be stated)

6- Was onco-neuronal antibody testing performed?
   Hu/Ri/Yo/Ma/Ta/GAD/Amphiphysin/VGKC/NMDA receptor etc

7- There is a statement in the discussion that EEG is not helpful in diagnosing LE etc – This statement is not true and requires referencing if it is to be kept in the manuscript.

8- Fig 5a: Axial FLAIR showing generalized, and predominantly subcortical areas of hyper-intensity, Fig 5b: Sagittal T2 showing frontal areas of hyper-intensity.

9- Lines 2-3 of introduction needs re-arranging. Some general grammatical errors need correcting.

Response:

1- Appropriate nomenclature for MRI has been included in the abstract (case presentation section) and manuscript (page 4, Line 17-19).

2- The patient collapsed while she was trying to move out of her chair. There was limited history available from the patient to exactly describe the mechanism of collapse, however, there was no history of witnessed seizures. Moreover, there was evidence of postural hypotension likely to be related to co-amiloizde she was on. We feel that postural blood pressure drop is the likely mechanism of patient’s collapse. The postural hypotension did improve after withdrawal of the drug and there were no further episodes of collapse.

3- ABG was not performed as there was no evidence of respiratory tract infection and she had adequate oxygen saturations (95% on breathing room air). AMT score of 7 was predominantly due to inability to recall and disorientation in time and place. However, a full MMSE or detailed neurological assessment was not performed.

4- Neurological examination amended with the addition of description of absence of signs suggesting cerebellopathy/peripheral neuropathy. Page 3, Paragraph 2.

5- Page 4, Paragraph 1. CT scan head with contrast, correction made.
6- Anti-neuronal antibodies. The CSF was sent for the antibody analysis, but unfortunately, due to inadequate preservation of sample/technical reasons, it could not be analysed for antibodies.

7- We do agree with the comment that EEG does provide useful information to support the diagnosis of LE, hence we have amended the sentence accordingly with an appropriate reference. Page 6, Paragraph 3.

8- MRI images and legends changed.


Kind Regards

Ahmed Fahim
Reviewer 2

Comment:

Dear Authors,

I appreciate your paper. I ask you to underline the antibody status of the patient if was done or please explain why it was not done.

Response:

Dear Dr Rizzardi,

Many thanks for reviewing our manuscript. Regarding the neuronal antibody status of the patient, the CSF was sent for the antibody analysis, but unfortunately, due to inadequate preservation of sample/technical reasons, it could not be analysed. We did not repeat the sample as we felt it would not have changed the management of our patient.

Kind Regards

Ahmed Fahim