

Dear Editor

Thank you very much for your decision letter and advice on our manuscript (Manuscript ID 81155) entitled “A rare case of Four kinds of antibody positive paraneoplastic limbic encephalitis and literature review”. We also thank the reviewers for the insightful comments and suggestions. Accordingly, we have revised the manuscript. All amendments are highlighted in red in the revised manuscript. In addition, point-by-point responses to the comments are listed below this letter.

We hope that the revision is acceptable for the publication in your journal.

Look forward to hearing from you soon.

With best wishes,

Yours sincerely,

Dr. Pan huang

We would like to express our sincere gratitude to the reviewers for their constructive and positive comments.

Replies to Reviewer 1 comments:

1. Thank you for providing this interesting manuscript. Here are my comments on this draft: - The case description is accurate, with enough details, and specific conclusions.

**Response:** We thank the reviewer for the positive comments.

2. Would be useful if authors could also discuss the evidence around using gamma globulins and high dose steroids in autoimmune paraneoplastic encephalitis.

**Response:** We thank the reviewer for the insightful suggestion.

3. Some of the language requires polishing as authors included terms without correspondence in English (e.g. 'advanced intelligent', 'reflex symmetry of the quadriplegic tendon', 'meninges stimulation').

**Response:** We thank the reviewer for the insightful suggestion. I have modified it and the manuscript was edited and proofread by a native English speaker.

4. Would be useful to add arrows on images to underlie the main abnormalities.

**Response:** We thank the reviewer for the insightful suggestion. I have added arrow indicators as per your request.

Replies to Reviewer 2 comments:

1. The authors have provided a systematic review on “a rare case with four kinds of antibody positive paraneoplastic limbic encephalitis”. The following comments are suggested: 1- Providing a Table by presenting the involved antibodies, the time, and the location of the central nervous system. 2- Emphasizing on the early detection. 3- Providing a brief methodology of the tests. 4- Providing complementary pedigree information in this regard. 5- Considering all the environmental factors, including nutrition. Furthermore, the final comment will unmask the severity and heterogenic pattern of the related antibodies by application of protein expression of the target antibodies in the Circulating Neural Cells, at single cell level, as early as possible, by observation of the initial symptom. \_Circulating Neural cells are assayable in 2 -3 ml of the peripheral blood.

**Response:** We thank the reviewer for the insightful suggestion. In this case, the patient's blood and cerebrospinal fluid were tested for the following antibodies: NMDAR, LGI1,

GABA<sub>B</sub>R, CASPR2, LgLON5, AMPAR, DPPX, GABA<sub>A</sub>R, mGluR5, synaptophysin-3 $\alpha$ , D<sub>2</sub>R, GlyR, GAD, AK5, Hu, CV2, Ma2, KLHL11. Anti-neuronal surface antigen antibodies and Some anti-synaptic intracellular antigen antibodies (e.g. GAD antibodies) The main method used is the indirect immunofluorescence assay (IIF). immunofluorescence assay (IIF). Depending on the antigen substrate cell based assay (CBA) and tissue based assay (TBA). As some of the information requested by the reviewers was not collected in this case report, we will take care in these areas in the future. Nonetheless, this case is still rarely seen and has greater relevance for clinical guidance.

Replies to Reviewer 3 comments:

3.This manuscript is a case report of a case of lung small cell carcinoma with para neoplastic encephalitis which is positive for four kind of antibody (a rare phenomenon). The overall quality is very good and can be considered for publishing with general priority.

**Response:** We thank the reviewer for the positive comments. We hope that the revision is acceptable for the publication in this journal.

We do not know if our the revised manuscript is enough to satisfy the reviewer. If our revised manuscript have some problems, please let us know.