

Anti-AMPA receptor encephalitis with myasthenia gravis: A sinister combination associated with a high risk for underlying malignancy

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Abstract

A rare subtype of autoimmune encephalitis consists of antibodies targeting the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor in the central nervous system. We describe the clinical presentation and autoimmune profile of the first case of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor encephalitis with concurrent anti-acetylcholine receptor antibodies in Pakistan. The patient was a 58-year-old male who presented with the characteristic symptoms of limbic encephalitis with memory loss, irritability, agitation, and confusion. Antibodies against the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor were detected in both serum and cerebrospinal fluid by indirect immunofluorescence. Computerised tomography of the chest showed an anterior mediastinal mass. The patient was treated with high dose Methylprednisolone and five sessions of plasma exchange. There was a short period of improvement; however, the patient now continues to exhibit irritability, aphasia, confusion, and memory loss. Video-assisted thoracoscopic surgery for mediastinal mass resection and histological testing was planned, however after review by the interventional radiologist the associated risks were deemed too high to proceed with the procedure and biopsy was not done.

Keywords: Autoimmune encephalitis, Limbic encephalitis, AMPA receptor encephalitis, Anti-acetylcholine receptor antibodies, Case report.

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Introduction

Autoimmune encephalitis is an immune-mediated disorder of the central nervous system associated with antibodies that target neuronal cell-surface or synaptic receptors and may present with or without cancer. Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor

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encephalitis is a rare subtype of autoimmune encephalitis where cell surface receptor antibodies are detected in the serum and cerebrospinal fluid. These receptors mediate excitatory synaptic transmission which are important for execution of cognitive functions.¹ The diagnostic findings for alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor encephalitis are the production of IgG antibodies against the GluA1 or GluA2 subunits of the receptor. It frequently presents as limbic encephalitis and is characterised by an acute or subacute onset of confusion, abnormal behaviour, seizure, and short-term memory loss.¹ Prompt treatment with immunotherapy and early treatment of neoplasms, if present, is important for a good prognosis.

To the best of our knowledge, we present the first case from Pakistan of a patient with autoantibody proven anti- alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor encephalitis with concomitant anti- acetylcholine receptor antibodies associated with a thymic mass. This case highlights the importance of prompt aggressive treatment of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor encephalitis, along with a thorough screening for underlying tumours, and other autoimmune antibodies, all of which contribute to a dismal prognosis.

Case Report

A 58-year-old male with no active comorbidity initially presented to a private hospital (Hameed Latif Hospital, Lahore) on June 3, 2023, with the complaints of disorientation in space and time along with fever for about a week. He had a three-month history of agitation, confusion, mutism, irritability, an episode of fits along with progressive loss of appetite resulting in a total weight loss of 18 kg. In addition, family members also noticed a decline in personal hygiene, decreased sleep and memory loss with inability to recognise family members over the last six weeks. There was a past history of cholecystectomy 12 years back and tuberculosis of the hip joint resulting in altered gait for the last six years.

The patient was undergoing treatment for encephalitis in the first hospital (Hameed Latif Hospital, Lahore) which was discontinued due to positive results for anti-Ro antibodies. Serum anti-nuclear antibodies showed a nucleolar pattern

with a titer of 1:80 suggesting neuro-Sjögren Syndrome. While the results for anti-SSA/Ro 52 antibodies were borderline positive (BlueDiver, Mons, Belgium), other test panel for extractable nuclear antigens were negative.

The patient was shifted to another private healthcare facility (Combined Military Hospital, Lahore) on June 7, 2023. On presentation, his vitals were stable, oxygen saturation was 92% and he was afebrile. Neurological examination revealed that his Glasgow Coma Scale³ (GCS) was 10/15 (E4M1V5), pupils were normal with purposeless eye tracking and increased generalised body tone. He was admitted to the medical intensive care unit and investigations were undertaken. Routine serum analyses were within the normal range. Hepatitis B/C and HIV were negative. C-reactive protein was 12.35mg/L (normal up to 5 mg/L). Cerebrospinal fluid analysis showed increased protein 66.5mg/dl (normal 15-45 mg/dl), while GeneXpert MTB and bacterial cultures on cerebrospinal fluid showed negative results.

Double lumen catheter was passed along with nasogastric tube on June 8. The patient was advised IV Solumedrol 1g OD for five days and plasma exchange was planned. Meropenem and Acyclovir were also started. The first plasma exchange session was done on June 8, however the patient remained unwell.

Cerebrospinal fluid sample was tested for IgG antibodies by indirect immunofluorescence using transfected EU 90 cells (Euroimmun, Luebeck, Germany) which was positive for alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antibodies on June 9 (Figure 1-A) and serum samples showed positivity at a serum dilution of 1:10 on June 21 (Figure 1-C). Antibodies were negative in both the serum and cerebrospinal fluid for N-methyl-D-aspartate receptor, gamma aminobutyric acid-B receptor, leucine-rich glioma inactivated 1, contact in-associated protein-like 2 and dipeptidyl-aminopeptidase like protein. Figure 1-B shows negative control for anti-AMPA receptors.

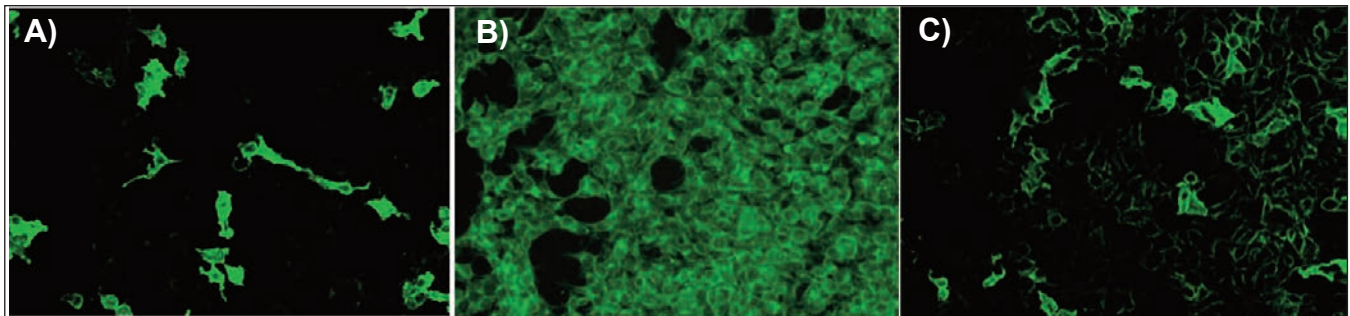


Figure-1: Photomicrograph stained by indirect immunofluorescence (objective 20x) showing: A) Patient's CSF positive for anti-AMPA antibodies (dated 09-06-23) tested neat on U90 cell line transfected with AMPA1/2-R gene clearly showing positivity with bright green fluorescent reaction. B) CSF negative control for anti-AMPA antibodies (dated 09-06-23) tested neat on U90 cell line transfected with AMPA1/2-R gene showing no staining. C) Patient's serum positive for anti-AMPA antibodies (dated 21-06-23) tested dilution 1:10 on U90 cell line transfected with AMPA1/2-R gene clearly showing positivity with bright green fluorescent reaction.

In addition, anti-neuronal profile for the detection of autoantibodies to nine different intracellular antigens (Amphiphysin, CRMP5, PNMA 2, Ri/ANNA-2, YO/PCA-1, Hu/ANNA-1, Recoverin, SOX1, Titin) in serum sample using Euroline immunoblot assay (Euroimmun, Lubeck, Germany) was negative.

Test for COVID-19 anti-spike IgG antibodies (Roche, Basel, Switzerland) was reactive 83.4 BAU/ml (normal less than 7.1 BAU/ml) which may indicate infection two to three weeks ago and high-resolution computed tomography was suggestive of inflammatory changes in the left lower zone.

On June 10, contrast enhanced magnetic resonance imaging of the brain was done which showed age-related atrophic changes; however, contrast enhanced CT of the abdomen, chest, and pelvis done on June 12 revealed an anterior mediastinal mass in the region of the thymus, a right thyroid nodule and an enlarged prostate.

Immediate suspicion of thymoma was raised and repetitive nerve stimulation/ electromyography-nerve conduction studies (RNS/EMG-NCS) were advised and the results for NCS were positive for neuromuscular fatigability, while serology was positive for anti-AchR antibodies (Euroimmun, Lubeck, Germany). The diagnosis of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor-associated encephalitis with myasthenia gravis was made.

The fifth and final plasma exchange session was done on June 13 after which the patient was shifted to the ward. The patient was started on Pyridostigmine for myasthenia gravis. GCS dropped to 8/15 on June 15 and Solumedrol was advised weekly for eight weeks.

Due to the proximity of the mediastinal mass to the right main pulmonary artery, CT guided biopsy was not undertaken. The multidisciplinary team including thoracic surgeon, neuro-physicians and family physician decided on

video-assisted thoracoscopic surgery after two to three weeks. The patient's condition showed improvement, and additional investigations for paraneoplastic syndrome were not pursued. The patient was discharged and scheduled for follow-up on an outpatient basis. However, following assessment by the interventional radiologist, it was determined that the risks associated with video-assisted thoracoscopic surgery (VATS) were too high to proceed with the procedure and biopsy was not done. The size of the growth remained consistent on MRI over a span of seven months and the medication was tapered off.

Discussion

Autoimmune encephalitis is an immune-mediated disorder associated with antibodies against extracellular or synaptic proteins with an acute or subacute presentation. A rare subtype of autoimmune encephalitis known as alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor encephalitis was first reported by Lai et al in 2009.^{4,5} The alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antibodies target the cell surface receptors which mediate excitatory synaptic transmission⁶ causing their degradation and internalisation which ultimately results in decreased AMPAR mediated current.⁷

It typically presents as limbic encephalitis (55%), characterised by confusion, abnormal behaviour, seizure, and short-term memory loss^{8,9} and is frequently associated with a tumour (60.6%) where thymoma accounts for 40%, small cell lung cancer (20%), breast cancer (16%), and ovarian cancer (7.5%).^{10,11}

In this patient, limbic encephalitis was the predominant presenting feature with seizures. Anterior mediastinal mass along with positive anti-acetylcholine receptor antibodies and EMG-NCS suggestive of a neuromuscular junctional disorder is highly indicative of an associated thymoma.

Although there were no significant findings in the CEMRI of the brain of this patient, the importance of neuroimaging in diagnosis of autoimmune encephalitis cannot be overlooked. In the absence of neuroimaging changes, the diagnosis relies on serum and cerebrospinal fluid antibodies.

A crucial feature of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor encephalitis is its tendency to relapse. A study conducted by Lai et al. revealed nine relapsing episodes in five patients and all were linked with the presence of GluA1/2 antibodies in serum or cerebrospinal fluid.

Another key distinguishing feature of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor

encephalitis is its partial recovery. A study published by Höftberger et al. revealed that 48% of the patients who responded to immunotherapy and oncological treatment showed partial neurological response and required a much more aggressive treatment in comparison to other types of autoimmune encephalitis such as N-methyl-D-aspartate receptor, gamma aminobutyric acid-B receptor or leucine-rich glioma inactivated1.⁹

Treatment of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor encephalitis encompasses both immunotherapy as well as oncological treatment. First-line treatment includes high-dose steroids, intravenous immunoglobulins, and plasma exchange. Patients who respond poorly to first line treatment may require second line treatment with Rituximab and Cyclophosphamide.⁸ Some patients also need aggressive anti-seizure medication, while oncological treatment includes chemotherapy, radiotherapy, and tumour resection.

This patient received high-dose intravenous Methylprednisolone and five sessions of plasma exchange. He began to show improvement with recognition of family members and was discharged with follow up on outpatient basis.

A recent study showed mortality rate of anti- alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor encephalitis to be 16% which can increase to 85% in patients with tumour and additional paraneoplastic autoimmunity.^{5,12}

Conclusion

Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor encephalitis usually presents as limbic encephalitis. Detection of GluA1/2 AMPAR antibodies should prompt aggressive treatment with extensive screening for underlying tumours, and other autoimmune antibodies, the presence of which have a poor prognosis. Immediate treatment and immunotherapy are important, and the high risk of relapse should be kept in mind, because the disorder is reversible, yet carries a very poor prognosis with an unacceptably high mortality rate of up to 85%.

Consent: Verbal consent was obtained from the brother of the patient for publishing his case as the patient was disoriented and unable to provide consent.

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References

1. Henley JM, Wilkinson KA. AMPA receptor trafficking and the mechanisms underlying synaptic plasticity and cognitive aging. *Dialogues Clin Neurosci* 2013;15:11-27. doi: 10.31887/DCNS.2013.15.1/jhenley.
2. Zhang TY, Cai MT, Zheng Y, Lai QL, Shen CH, Qiao S, et al. Anti-Alpha-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid Receptor Encephalitis: A Review. *Front Immunol* 2021;12:e652820. doi: 10.3389/fimmu.2021.652820.
3. Jain S, Iverson LM. *Glasgow Coma Scale*. Treasure Island, FL: StatPearls Publishing; 2024.
4. Lai M, Hughes EG, Peng X, Zhou L, Gleichman AJ, Shu H, et al. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. *Ann Neurol* 2009;65:424-34. doi: 10.1002/ana.21589.
5. Laurido-Soto O, Brier MR, Simon LE, McCullough A, Bucelli RC, Day GS. Patient characteristics and outcome associations in AMPA receptor encephalitis. *J Neurol* 2019;266:450-60. doi: 10.1007/s00415-018-9153-8.
6. Shepherd JD, Huganir RL. The cell biology of synaptic plasticity: AMPA receptor trafficking. *Annu Rev Cell Dev Biol* 2007;23:613-43. doi: 10.1146/annurev.cellbio.23.090506.123516.
7. Peng X, Hughes EG, Moscato EH, Parsons TD, Dalmau J, Balice-Gordon RJ. Cellular plasticity induced by anti- α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor encephalitis antibodies. *Ann Neurol* 2015;77:381-98. doi: 10.1002/ana.24293.
8. Dalmau J, Vincent A. Do we need to measure specific antibodies in patients with limbic encephalitis? *Neurology* 2017;88:508-9. doi: 10.1212/WNL.0000000000003592.
9. Höftberger R, van Sonderen A, Leypoldt F, Houghton D, Geschwind M, Gelfand J, et al. Encephalitis and AMPA receptor antibodies: Novel findings in a case series of 22 patients. *Neurology* 2015;84:2403-12. doi: 10.1212/WNL.0000000000001682.
10. Tirthani E, Said MS, Smith RG, Jadhav N, Shanina E. Paraneoplastic Encephalomyelitis. Treasure Island, FL: StatPearls Publishing; 2024.
11. Song W, Li K, Li J, Liu X, Wu X, Xu X, et al. Thymoma-associated autoimmune encephalitis: Analysis of factors determining prognosis. *CNS Neurosci Ther* 2023;29:1213-21. doi: 10.1111/cns.14166.
12. Panzer JA, Dale RC. Anti-AMPA receptor encephalitis: The family of glutamatergic autoencephalitides further expands. *Neurology* 2015;84:2390-1. doi: 10.1212/WNL.0000000000001693.

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TM: Composed and drafting.

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MQ, FJ: Drafting.

TAA: Concept, review and final approval.