A RARE ASSOCIATION OF ANTI- GABA-B RECEPTOR WITH ANTI-HU ANTIBODIES IN AUTOIMMUNE ENCEPHALITIS: A CASE REPORT

Tahira Mohammad, Muhammad Amjad, Aftab Akhtar, Tahir Aziz Ahmed

Shifa International Hospital, Islamabad Pakistan

ABSTRACT

Antibodies to the gamma-aminobutyric acid-B receptor (Anti-GABA-B-R) mediate an uncommon subtype of autoimmune encephalitis (AE) in which IgG antibodies directed against the B1 subunit of the GABA-B-R has been described. Clinically it presents as limbic encephalitis (LE) which is characterized by seizures, psychosis, and memory loss with progression to autonomic dysfunction, altered consciousness, and death. We present a case of an elderly male who presented in the ER due to progressive agitation, confusion, and irritability. Immunological workup revealed anti-GABA-B-R and anti-Hu antibodies. After admission, his consciousness rapidly deteriorated over the next few days, and he was intubated. The patient developed septic shock and due to poor prognosis, the patient's family requested withdrawal of ventilatory support.

Key Words: Autoimmune encephalitis, Limbic encephalitis, Paraneoplastic antibody, GABA B receptor, anti-Hu antibody, Septic shock.

This case report can be cited as: Mohammad T, Amjad M, Akhtar A, Ahmed TA. A rare association of anti- gaba-B receptor with anti-HU antibodies in autoimmune encephalitis: A case report. Pak J Pathol. 2022; 33(1): 40-42.

DOI: 10.55629/pakjpathol.v33i1.702.

INTRODUCTION

Immune-mediated disorders of the central nervous system (CNS) include the classic paraneoplastic neuronal syndromes (PNS) and AE. The PNS are relatively rare, are most often associated with malignancy and the associated antibodies target intracellular neuronal antigens which most likely mediate T-cell responses. Antibodies associated with autoimmune encephalitis target neuronal cell-surface or synaptic receptors and mediate their effects through humoral mechanisms. AE may present with or without cancer.

Anti-GABA-B-R encephalitis is rare and accounts for approximately 5% of all cases of LE [1]. It was first described by Lancaster et al. [2] and is one of the subtypes of autoimmune encephalitis. GABA-B-R antibodies are surface receptor antibodies and are highly specific and sensitive diagnostic markers. The diagnostic findings are the production of IgG antibodies against the B1 subunit of the GABA-B receptor [2]. GABA-B-R encephalitis clinically presents as seizures in 90%, cognitive impairment in 85%, altered consciousness in 70%, psychiatric symptoms in 70%, lung infections in 50% and respiratory failure with mechanical ventilation in 25% [3]. Atypical presentations of anti-GABA-B-R encephalitis include ataxia and opsoclonus-myoclonus syndrome [4]. According to one report from India, anti-GABA-B-R encephalitis can also present with orthostatic hypotension due to autonomic dysfunction [5]. Published literature shows that the average onset age of anti-GABA-B receptor encephalitis is 60~70 years. Of clinical importance is that the GABA-B receptor has been described as an autoantigen of paraneoplastic and nonparaneoplastic LE. Small-cell lung cancer (SCLC) was identified in 50% of patients, all with LE-associated GABA-B encephalitis and neurologic syndrome preceded the diagnosis of SCLC in 90% of cases [4]. Thus, tumor screening and treatment is essential to proper management. The gold standard for diagnosing anti-GABA-B receptor encephalitis is autoantibody testing in either serum or cerebrospinal fluid (CSF). Early diagnosis and prompt immunomodulating treatment may provide a good outcome and alter the course of this potentially lethal albeit treatable cause of encephalitis.

Previous reports have established the co-existence of additional antibodies in patients with anti-GABA-B-R associated encephalitis [4] including anti-Hu which is one of the most well recognized onconeural antibodies.

Anti Hu antibodies were first identified by Graus et al. [6] Anti-Hu is an onconeural antibody to intracellular antigens and is most frequently seen in patients with PNS. Anti-Hu-associated neurologic syndromes include sensory neuropathy (54%), cerebellar ataxia (10%), limbic encephalitis (9%), and

Correspondence: Dr Tahira Mohammad, Department of Pathology, Shifa International Hospital Islamabad Pakistan

Email: **tahiramo2001@gmail.com**

Received: ***03 Feb 2022****; Revised:* ***26 Feb 2022****; Accepted:* ***16 Mar 2022***

multifocal involvement (11%) [7]. According to literature, the association of anti-Hu with SCLC is 74% [7]. The neurological symptoms often precede the detection of the associated malignancy if present. Thus, the presence of onconeural antibodies can help determine the presence of cancer. Immunotherapy may improve symptoms however prognosis is poor.

We present a rare case from Pakistan of a patient with autoantibody proven anti-GABA-B receptor encephalitis with concomitant anti-Hu antibodies.

CASE PRESENTATION

This is a case of a 61-year-old male who was an ex-smoker with hypertension and diabetes for the last 20 years. He had a 2-month history of progressive restlessness in both legs. For the last 2-3 weeks he was seeing a psychiatrist who put him on anti-psychotics for severe irritability and later confusion. However, there was no improvement in symptoms, and he was brought to the ER. There was no history of fever, headache, or vomiting, although he had weight loss in the last month. Upon admission his Glasgow Coma Scale (GCS) was 10/15; Heart Rate 108 beats/minute; Blood Pressure 121/70 mm Hg; Respiratory rate 18 breaths/min; Oxygen saturation 92% and he was afebrile. Neurological examination showed that he was confused but was able to follow one-step commands on repetitive stimulation. Pupils were equal and reactive to light and his eye movements were conjugate. There was no facial asymmetry, and he was moving all four limbs. Reflexes were all 2+ and plantar responses were flexor on both sides. There was no sign of meningeal irritation. On arrival his computerized tomography (CT) brain without contrast was performed which was unremarkable. Later magnetic resonance imaging (MRI) with contrast was planned but could not be performed due to irritability and confusion.

Considering the possibility of encephalitis, work up for meningoencephalitis was done and the meningitis pathway was activated. Cerebrospinal fluid (CSF) analysis showed white blood cells 6/UL, neutrophils 60%, blood glucose 90.3mg/dl, and protein 310.4mg/dl. Gram stain of CSF, MTB DNA by PCR, and HSV by PCR were negative. The immunological workup revealed anti-GABA-B-R antibodies and anti-Hu antibodies. CSF was tested for anti-GABA-B-R IgG antibodies by indirect immunofluorescence (IIF) using EU 90 cells transfected with GABA B1/B2 as substrate that is fixed on slides (prepared by Euroimmun, Luebeck, Germany). Slides were incubated with CSF samples (undiluted) for thirty minutes and then washed and stained with fluorescein-labeled anti-human IgG antibodies and analyzed using a fluorescence microscope. In addition, anti-neuronal profile for the detection of autoantibodies to 9 different intracellular antigens in serum sample using Euroline immunoblot assay (prepared by Euroimmun, Lubeck, Germany) revealed anti-Hu antibodies.

Chest CT with contrast was negative for primary neoplasm and metastatic lesions. However, changes were observed that suggested an infective process. It is noteworthy that the patient had fully recovered from COVID-19 five months ago for which he was hospitalized. At present, he tested negative for SARS-CoV-2 by polymerase chain reaction (PCR). CT abdomen and pelvis were also unremarkable. In addition, there were no significant intracranial abnormalities detected on CT brain. The patient underwent two sessions of therapeutic plasma exchange (PLEX) along with pulsed steroids following which he had a sudden drop in GCS for which the patient was intubated. He was shifted to Medical ICU with a GCS of 3/15. On neurological examination, his pupils became fixed, dilated and doll's eye reflex was absent along with atony with absent gag and cough reflex. On the 5th day of admission, tracheal culture was positive for Pseudomonas Aeruginosa and E. Coli. The patient went into shock and his total leukocyte count increased from 7370/microliter to 15820/microliter. He was started on ionotropic support; however, he was unable to maintain blood pressure. Ultimately due to poor prognosis compounded by septic shock with end-organ failure, the patients' family requested withdrawal of ventilatory and ionotropic support. The patient died of cardiopulmonary arrest 6 days after admission.

DISCUSSION

Research on AE remains sparse in South Asia and the cases are underreported. We present a fatal case of autoimmune encephalitis with the presence of dual antibodies (anti-GABA-B-R receptor and anti-Hu). This is notable as only a handful of patients have previously been described with this combination. Studies from China report 8 cases with a combination of anti-GABA-B-R and anti-Hu antibodies [8-11]. Published literature shows the presence of both GABA-B-R antibodies and Hu antibodies is rare with a prevalence of 3% [8]. Our patient was an elderly male and presented with symptoms of altered sensorium, irritability, and confusion which is consistent with the published data,

according to which 64% of the reported anti-GABA-B-R encephalitis cases present with behavioral abnormalities [9].

Despite the presence of both anti-GABA-B encephalitis and anti-Hu paraneoplastic antibodies, our patient was negative for an associated neoplasm. On CSF analysis, our patient had increased protein, which is in line with published literature where 36% of patients had elevated CSF protein [9]. AE caused by cell surface receptor antibodies are humorally mediated and respond to immunotherapy however, antibodies against intracellular antigens, which usually indicate cytotoxic T-cell mechanisms are less responsive [12]. Our patients' treatment included pulsed steroids and he underwent two sessions of PLEX.

A published report from Shifa International Hospital of 2 cases of GABA -B-R encephalitis by Niazi *et al* [13] showed that patient 1 presented with symptoms of memory dysfunction and patient 2 presented with behavioral problems. Both patients were negative for malignancy as was our patient. The test result of patient 1 for antibodies against intracellular neuronal antigens including titin, SOX-1, Recoverin, Hu, Yo, Ri, CV2, Amphiphysin, and PNMA2 was negative in contrast to our patient who had a positive test result for anti-Hu antibodies. Patient 1 fully recovered on oral and parenteral steroids whereas patient 2 did not show improvement with steroids or plasma exchange. Similarly, our patient did not improve with steroids and PLEX.

CONCLUSION

In conclusion, we present a rare case diagnosed as AE with anti-Hu and anti-GABA-B-R antibodies. A high index of suspicion should be raised specifically in elderly males with altered sensorium, behavioral change, and irritability followed by altered consciousness. Immunotherapy can improve the neurological function of patients with GABA-B-R encephalitis. However, older age, delayed improvement after immunotherapy, respiratory failure, and shock may be associated with fatal outcomes.

ACKNOWLEDGMENTS

We would like to acknowledge Dr. Arsalan Ahmed Consultant Neurologist for his contribution to this study.

AUTHORS CONTRIBUTION

Tahira Mohammad: Composed and drafted the repot

Muhammad Amjad and Aftab Akhtar: Review of clinical data, assisted in drafting

Tahir Aziz Ahmed: Conception, critical revision, and final approval

REFERENCES

1. Lancaster E, Martinez-Hernandez E, Dalmau J. Encephalitis and antibodies to synaptic and neuronal cell surface proteins. Neurol. 2011;77(2):179-89.
2. Lancaster E, Lai M, Peng X, Hughes E, Constantinescu R, Raizer J, *et al*. Antibodies to the GABAB receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. Lancet Neurol. 2010;9(1):67-76.
3. Wen X, Wang B, Wang C, Han C, Guo S. A retrospective study of patients with GABABR encephalitis: Therapy, disease activity and prognostic factors. Neuropsychiatric Dis Treatment. 2021;17:99-110.
4. Hoftberger R, Titulaer M, Sabater L, Dome B, Rozsas A, Hegedus B, *et al*. Encephalitis and GABAB receptor antibodies: Novel findings in a new case series of 20 patients. Neurol. 2013;81(17):1500-1506.
5. Pradhan S, Das A, Das A, Mulmuley M. Antibody negative autoimmune encephalitis- Does it differ from definite one? Annals of Indian Academy Neurol. 2019;0(0):0.
6. Graus F, Cordon-Cardo C, Posner J. Neuronal antinuclear antibody in sensory neuronopathy from lung cancer. Neurol. 1985;35(4):538-538.
7. Graus F. Anti-Hu-associated paraneoplastic encephalomyelitis: analysis of 200 patients. Brain. 2001;124(6):1138-48.
8. Lin J, Li C, Li A, Liu X, Wang R, Chen C*, et al*. Encephalitis with antibodies against the GABAB receptor: high mortality and risk factors. Front Neurol. 2019;10.
9. Zhu F, Shan W, Lv R, Li Z, Wang Q. Clinical characteristics of Anti-GABA-B receptor encephalitis. Front Neurol. 2020;11.
10. Zhang X, Lang Y, Sun L, Zhang W, Lin W, Cui L. Clinical characteristics and prognostic analysis of anti-gamma-aminobutyric acid-B (GABA-B) receptor encephalitis in Northeast China. BMC Neurol. 2020;20(1).
11. Guan H, Ren H, Yang X, Lu Q, Peng B, Zhu Y et al. Limbic encephalitis associated with anti-γ-aminobutyric acid B receptor antibodies. Chinese Med J. 2015;128(22):3023-28.
12. Graus F, Saiz A, Lai M, Bruna J, Lopez F, Sabater L *et al.* Neuronal surface antigen antibodies in limbic encephalitis: Clinical-immunologic associations. Neurol. 2008; 71(12): 930-36.
13. Niazi AK, Shaikh S, Ahmad A, Zafar A, Ahmed TA. Gaba-B Encephalitis in Pakistan: A Rare but Treatable Entity. Pak J Neurolog Sci. 2021;16(2):16-18.