Int. j. adv. multidisc. res. stud. 2024; 4(3):1666-1669

Received: 09-05-2024
Accepted: 19-06-2024

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

Glycine Receptor Antibody-mediated Autoimmune Encephalitis: A Case Report

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Abstract

Background: Glycine receptor (GlyR) serves a significant inhibitory function within the neurological system. It may be targeted by autoantibodies which might lead to autoimmune synaptic encephalitis (AE). It can also be associated with other autoimmune diseases, thereby adding complexity to its clinical manifestations and treatment approaches. In this case we present a vegetative condition of a man with GlyR antibody mediated AE.

Case presentation: A 38-year-old previously healthy male, experienced muscular spasms, olfactory and auditory hallucinations, as well as sleep disturbances. He was admitted to the hospital due to his right-sided mouth deviation and severe myoclonic jerks. Subsequently, he suffered a cardio-respiratory failure, leading to a coma. GlyR antibodies were then identified in his serum confirming a diagnosis of anti-GlyR encephalitis. Additionally, his symptoms led to a concurrent diagnosis of progressive encephalomyelitis with rigidity and myoclonus (PERM). He was administered steroids, immunoglobin therapy, and plasma exchange therapy. His brain MRI showed severe atrophy. After a period of follow-up, the patient remained in a vegetative state, awake but lacking awareness of his surroundings.

Conclusion: The incidence of GlyR antibody-associated encephalitis is low. The diverse array of symptoms, resulted in a delay in diagnosis and subsequent treatment in our patient's case, consequently leading to unfortunate complications.

Keywords: Autoimmune Encephalitis, Glycine Receptor Antibody, Progressive Encephalomyelitis with Rigidity and Myoclonus, Vegetative, Case Report

1. Introduction

Autoimmune encephalitis (AE) is considered an immune-mediated disease that causes brain inflammation and ranks among the most common causes of non-infectious encephalitis [1]. Autoimmune encephalitis linked to Glycine receptor (GlyR) antibody was first identified in 2008, originally described in a patient with progressive encephalomyelitis characterized by rigidity and myoclonus (PERM) [2]. Variations in clinical presentation and the occurrence of nonsequential multiphasic episodes often result in diagnostic delay [3]. GlyR plays a significant role as an inhibitory neurotransmitter, crucial for preventing excessive neural excitability [4]. The symptoms of GlyR dysfunction are intense muscle spasms, stiffness, seizures, myoclonus, autonomic instability, sensory symptoms, and respiratory failure [5]. Within this context, we present a case report detailing the condition of a 38-year-old gentleman who presented with sleep disturbances, olfactory hallucinations, and recurrent seizures. The diagnosis indicated GlyR antibody-associated encephalitis, with PERM symptoms and no concurrent stiff man syndrome.

2. Case Report

A 38-year-old healthy man, with no prior medical history presented to the emergency department (ED) in mid-April 2023, with severe myoclonic jerks, mouth deviation, and speech disturbances. Preceding this he had experienced a one-month history of progressive sleeplessness, diminished appetite, olfactory hallucinations (as a "fetid smell"), auditory hallucinations, and muscular spasms.

As these previous symptoms continued to worsen, he had more emotional disturbances and he underwent a comprehensive neurological examination which was normal. Similarly, his brain magnetic resonance imaging (MRI) did not show any abnormalities. Initially, he was misdiagnosed with a severe depression. Subsequently, due to his persistent sleeplessness, he

went to the Emergency Department (ED) and was administered a Midazolam injection. The day after receiving the injection, he started to have excessive vasovagal symptoms which culminated in his first-ever panic attack. This was followed by a brief episode of right-sided mouth deviation and myoclonic seizures prompting his admission into the ED in Jordan.

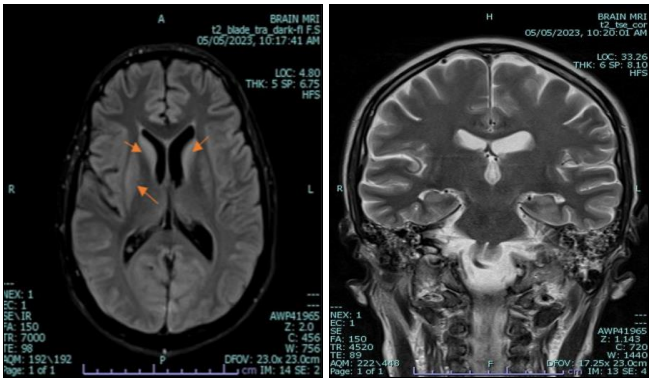
In the first three days of his admission, he was prescribed anti-seizure medications to reduce his abrupt spasms and numbness. His wife also reported an instance of his hand experiencing involuntary spasms, and his electroencephalography (EEG) was normal. Then he suddenly had a cardiac-respiratory failure. It took five cycles of resuscitation before his condition stabilized, eventually resulting in his entry into a coma, which necessitated his transfer to the intensive care unit (ICU) for further management.

He experienced status epilepticus and was administrated IV antiepileptic drugs during the initial weeks following his admission to the ICU to manage persistent seizures during his coma. Subsequently, his status epilepticus condition resolved with the help of medications. His cerebrospinal fluid (CSF) analysis revealed normal protein and red blood cell (RBC) count while displaying increased white blood cell (WBC) counts, neutrophils, and lymphocytes. Notably, there was a significant decrease in his monocyte levels (5%, as opposed to the normal reference range of 15%-45%). However, tests for serum measles, herpes simplex virus (HSV), Antineuronal nuclear antibody type 1 (ANNA-1), Antineuronal nuclear antibody type 2 (ANNA-2), Purkinje cell cytoplasmic antibody 1 (PCA-1), and glutamic acid decarboxylase 65 (GAD-65), all returned negative results. However, he has elevated levels of C-reactive protein (CRP). His liver function tests revealed elevation in alanine aminotransferase (ALT), and aspartate aminotransferase (AST). Also, an MRI brain was done initially at the beginning of May 2023 while he was comatose revealing abnormal signals in the head of the caudate nucleus and putamen nucleus (Fig 1). EEG showed severe diffuse slowing waves (delta wave).

Autoimmune antibodies targeting neuronal cell-surface and synaptic proteins, including NMDAR, AMPAR, mGluR1, mGluR5, GABA-B R, and LGI-1, yielded negative results in serum testing. However, GlyR antibodies were identified in the serum, confirming the diagnosis of anti-GlyR encephalitis. Intravenous methylprednisolone (1 gm/day, for 5 days) treatment was initiated empirically before the detection of GlyR antibodies, prompted by the physician's suspicion of autoimmune encephalitis. This was followed by plasma exchange therapy (5 sessions, every other day), and finally, he was treated with intravenous immunoglobulin (IV-IG) (0.4 gr/kg daily for 5 days). These were the first lines of immunotherapy which were administrated as per the treatment plan. Unfortunately, the second-line treatment (Rituximab & cyclophosphamide) could not be applied as the patient remained unresponsive, preventing the medical team from assessing the efficacy of these drugs. Notably, due to his symptoms, he was also diagnosed with PERM due to his anti-GlyR encephalitis.

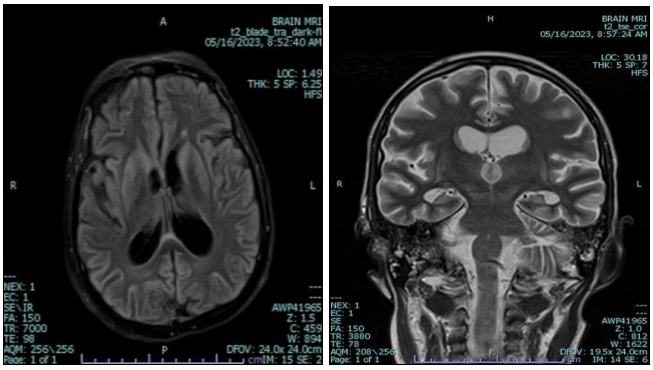
The patient underwent a laparoscopy and had a percutaneous endoscopic gastrostomy (PEG) tube inserted into his abdomen enabling him to be able to receive the necessary food and nutrients. Then, complications arose as he developed an infection at the PEG tube site, which as a result led him to have a methicillin-resistant staphylococcus aureus (MRSA) infection through which he was given Vancomycin hydrochloride and Meropenem. Furthermore, a tracheostomy tube was inserted enabling the gradual reduction of ventilator support. Repeat EEG examination findings were unchanged compared to the previous recording i.e. showing diffuse slowing. Two brain MRIs were done at the end of May (**Figure 2A**) and later in June (**Figure 2B**), revealing signs of brain atrophy and abnormal signals in the cerebral cortex as well as white matter as illustrated in Fig 2.

After a period of follow-up, he was able to be transferred out of the intensive care unit (ICU). He remains in a non-alert and non-oriented state, rendering him unable to respond to commands. This state is commonly referred to as vegetative state, that is he is awake but non-aware of the surroundings. In this state, he is capable of opening his eyes, cycling through normal sleep-wake patterns, and exhibiting basic reflexes. He is currently prescribed Levetiracetam and Valproic acid to manage and prevent seizures.

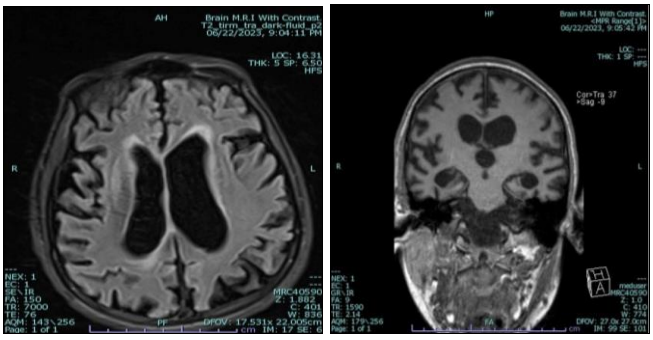


1A **1B**

Fig 1: Initial axial flair (**Fig. 1A**) and coronal T2- weighted images (**Fig. 1B**) demonstrated diffuse abnormal signal in cerebral cortex and deep gray matter (head of caudate and less evident in putamen nucleus)



A



B

Fig 2: Axial flair and coronal T2 at the end of May (**Fig. 2A**) as well as axial flair and coronal T1 done about one-month latter (**Fig. 2B**) demonstrating severe atrophy with progression of abnormal signal in cerebral cortex and white matter due to the known encephalitis

3. Discussion

Glycine receptor (GlyR) antibody-associated illness typically manifests with central nervous system (CNS) hyperexcitability, myoclonus, hyperekplexia, autonomic dysfunction, and respiratory failure [5, 6]. These manifestations may present as acute or subacute symptoms. Among the diverse spectrum of disorders associated with GlyR antibodies, the most prevalent forms are stiff person syndrome and PERM [7]. Our case represents AE associated with GlyR fulfilling the diagnostic criteria for PERM, although the diagnosis was delayed.

PERM represents one of the most common phenotypes associated with GlyR antibodies. PERM is characterized by limb and truncal rigidity, stimulus-sensitive spasms, autonomic disturbances, and involvement of the brainstem or other neurological deficits [5]. Notably, Yana Su *et al.* observed a male predilection in PERM cases without a clear underlying reason. They reported a case of PERM co-occurring with thymoma, which tested positive for anti-glutamic acid decarboxylase (anti-GAD) antibodies. GAD enzymes are known to catalyze the conversion of glutamic acid to gamma-aminobutyric acid (GABA) [8], therefore GAD antibodies lead to the accumulation of glutamic acid which is considered an excitatory neurotransmitter, thus leading to the symptoms of rigidity and myoclonus. However, it is important to note that our patient did not exhibit the presence of anti-GAD antibodies, a feature commonly found in PERM and stiff-person syndrome (SPS) cases. Furthermore, some GlyR–IgG–positive patients have been linked to various tumors, including thymoma [9]. Nevertheless, our patient did not present any clinical or paraclinical evidence of tumor involvement.

Our case presents a one-month history of olfactory hallucinations, myoclonus, rigidity, and sleep disturbances. These symptoms subsequently worsened, resulting in right mouth deviation and severe spasms leading to the patient's admission to the hospital. Then he suffered a cardiorespiratory arrest leading to a coma and subsequently a vegetative state. A previous report showed that respiratory failure contributes to some of the rare fatal cases of GlyRab-mediated AE [5]. Unfortunately, despite these alarming symptoms, the patient had not yet been diagnosed, which caused a delay in initiating therapy. Conversely, a fatal case of GlyR AE has been reported in literature, featuring a man with significant brainstem involvement but lacking muscular rigidity or spasms [10].

In addition, our patient did not exhibit typical symptoms or distinctive clinical signs associated with the specific illness. In contrast to LGI-1 antibody-associated encephalitis, which ranks as the second most prevalent form of AE following NMDA antibody-associated encephalitis, individuals typically present with facial-brachial dystonic seizure (FBDS). FBDS is recognized as one of the hallmark manifestations of LGI-1 antibody-associated encephalitis [11].

Various triggers have been investigated for their potential contribution to the onset of the disease. One notable trigger is the history of previous infections such as herpes simplex encephalitis (HSE). A previous observational study reported that 27% of AE cases occur after a prior episode of HSE [12, 13]. However, our patient showed negative results regarding the presence of HSV or any previous infection that might be associated with the current condition. Furthermore, when considering patients with GlyR-Abs, it is observed that approximately 25% of them have concomitant autoimmune conditions, while 10–20% exhibit an underlying malignancy, notably lymphomas [6]. It is pertinent to

mention that our case did not manifest any underlying tumor or concurrent autoimmune disease.

The serum sample was analyzed during the patient's comatose state, and the presence of GlyR-Ab was confirmed using immunofluorescence assays of transfected cells performed at Eurofins Biomnis laboratories in France. Concurrently, his MRI revealed a progressive pattern of cerebral atrophy while he remained in a comatose state. There was a delay in diagnosing his condition, and treatment was initiated based on clinical suspicion. Due to his persistently unconscious state, it remains challenging to assess whether he has exhibited any positive response to the initial treatment or whether consideration of second-line therapy is warranted.

In conclusion, this is a rare case that presented with a unique receptor antibody (GlyR-ab) coupled with symptoms such as sleep disturbances, olfactory hallucinations, and muscular rigidity. The variability in symptoms contributed to a delayed diagnosis and subsequent treatment initiation. It is imperative to emphasize the significance of timely diagnosis in such cases to mitigate the potential neurological damage associated with delays. The diagnostic approach should ideally encompass both serum and cerebrospinal fluid (CSF) analysis, as the detection of GlyR antibodies in CSF is considered more precise. However, in our patient's case, the diagnosis relied solely on serum testing. Additionally, it is crucial to recognize the risk of sudden cardiac arrest and respiratory failure in patients with AE, as these events can lead to life-threatening situations or comatose states. This awareness is essential to implement preventive measures and optimize patient outcomes.

4. Informed consent

Informed consent was obtained from the patient spouse.

5. Ethical approval

The ethics committee of Jordan University Hospital agreed that all ethical guidelines have been followed.

6. Data availability statement

The data that support this study cannot be publicly shared due to ethical or privacy reasons and may be shared upon reasonable request to the corresponding author if appropriate.

7. Conflict of interest

The authors declare no conflict of interest.

8. Declaration of funding

This research did not receive any specific funding.

9. Acknowledgment

None.

10. References

1. Shrey Gole, Amritpal Anand. Autoimmune encephalitis. Treasure Island (FL): StatPearls, 2023.
2. Hutchinson M. *et al.* Progressive Encephalomyelitis, Rigidity, and Myoclonus: A Novel Glycine Receptor Antibody. Neurology. 2008; 71(16):1291-1292. Doi: 10.1212/01.wnl.0000327606.50322.f0.
3. Ford B, McDonald A, Srinivasan S. Anti-NMDA receptor encephalitis: A case study and illness overview. Drugs in Context. 2019; 8:1-8. Doi: 10.7573/dic.212589.
4. Swayne A, *et al.* Antiglycine receptor antibody related disease: A case series and literature review. European Journal of Neurology. 2018; 25(10):1290-1298. Doi: 10.1111/ene.13721
5. Carvajal-González A, *et al.* Glycine receptor antibodies in PERM and related syndromes: Characteristics, clinical features and outcomes. Brain. 2014; 137(8):2178-2192. Doi: 10.1093/brain/awu142.
6. Crisp SJ, Balint B, Vincent A. Redefining progressive encephalomyelitis with rigidity and myoclonus after the discovery of antibodies to glycine receptors. Current Opinion in Neurology. 2017; 30(3):310-316. Doi: 10.1097/WCO.0000000000000450.
7. Rauschenberger V, *et al.* Glycine Receptor Autoantibodies Impair Receptor Function and Induce Motor Dysfunction. Annals of Neurology. 2020; 88(3):544-561. Doi: 10.1002/ana.25832.
8. Su Y, *et al.* Progressive Encephalomyelitis with Rigidity and Myoclonus with Thymoma: A Case Report and Literature Review. Frontiers in Neurology. 2020; 11:1017. Doi: 10.3389/fneur.2020.01017
9. Clerinx K, *et al.* Progressive encephalomyelitis with rigidity and myoclonus: Resolution after thymectomy. Neurology. 2011; 76(3):303-305. Doi: https://doi.org/10.1212/WNL.0b013e318207b008.
10. Reniers W, Ernon L, Bekelaar K. A fatal case of glycine receptor antibody-mediated autoimmune encephalitis. Acta Neurologica Belgica. 2021; 121(1):269-270. Doi: 10.1007/s13760-020-01590-1
11. Zhao J, *et al.* Leucine-rich glioma-inactivated protein 1 antibody-associated encephalitis in a 22-month-old girl: A case report. BMC Pediatrics. 2023; 23(1):389. Doi: 10.1186/s12887-023-04191-y
12. Armangue T, *et al.* Autoimmune post–herpes simplex encephalitis of adults and teenagers. Neurology. 2015; 85(20):1736-1743. Doi: 10.1212/WNL.0000000000002125
13. Armangue T, *et al.* Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: A prospective observational study and retrospective analysis. The Lancet Neurology. 2018; 17(9):760-772. Doi: 10.1016/S1474-4422(18)30244-8