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Salman Farooq
Khoula Hospital, Muscat Oman

Shafaq Saleem
Aga Khan University Hospital, Karachi

Muhammad Bilal Tariq
Aga Khan University Hospital, Karachi

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ROLE OF RITUXIMAB IN AUTOIMMUNE ENCEPHALITIS: A REPORT OF TWO CASES

Salman Farooq[1], Shafaq Saleem[2], Muhammad Bilal Tariq[2]
[1] Khoula Hospital, Muscat Oman
[2] Aga Khan University Hospital, Karachi

Corresponding Author: Shafaq Saleem *Aga Khan University Hospital, Karachi* ***Email:*** *drshafaqsaleem@gmail.com*

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ABSTRACT

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a form of autoimmune encephalitis that predominantly affects young individuals and often presents with neuropsychiatric symptoms. It is frequently misdiagnosed as a primary psychiatric disorder due to its initial presentation. Although first-line immunotherapy typically includes corticosteroids, intravenous immunoglobulin (IVIG), or plasmapheresis, a subset of patients shows limited response and requires escalation to second-line agents such as Rituximab. We report two adult male patients, aged 35 and 41 years, who initially presented with behavioral disturbances, confusion, memory deficits, and speech abnormalities. Both were initially misdiagnosed with psychiatric illnesses, delaying appropriate treatment. Diagnostic workups including MRI, EEG, and cerebrospinal fluid analysis were unremarkable; however, both patients tested positive for anti-NMDAR antibodies in serum and CSF. First-line immunotherapy with methylprednisolone and IVIG failed to yield significant improvement. Rituximab was subsequently initiated, leading to substantial clinical recovery in both cases. One patient experienced steroid-induced psychosis, which was resolved with psychiatric management. No Rituximab-related complications were observed. These cases highlight the importance of early consideration of anti-NMDAR encephalitis in adults presenting with acute psychiatric and cognitive symptoms. Timely diagnosis and escalation to second-line therapy with Rituximab in cases unresponsive to first-line treatment can significantly improve outcomes.

INTRODUCTION

Amongst the cases of viral encephalitis, anti-NMDAR is the most common, even surpassing viral etiologies in younger population.[1] Anti-NMDAR encephalitis was first described in 2005 after four young women with ovarian teratomas, presented with psychiatric symptoms and hypoventilation.[2] Since then, anti-NMDAR encephalitis has been recognized more frequently, accounting for nearly 25% of all cases of autoimmune antibodies.[3-5]

Anti-NMDAR encephalitis is three times more common in females than males and usually presents in younger patients with a median age in the early twenties.[6-7] Symptoms range from behavioral problems, memory loss, and seizures to hypoventilation. Due to the frequency of psychiatric symptoms, many patients are mistakenly diagnosed with a primary psychiatric disorder.[6-8] Diagnosis of anti-NMDAR encephalitis is based on clinical presentation followed by a demonstration of anti-NMDAR antibodies in the CSF. Treatment usually involves immunotherapy along with surgery for tumor removal if present.

Treatment of NMDAR encephalitis has evolved over years, with the use of second line immunotherapeutic agents for refractory cases, with relapses and maintaining remission. The choice to use any of them is purely on the discretion of physicians. The absence of large-scale studies limits the use of second line agents on their optimal timings, duration and the choice of medication. We report two cases of patients who did not respond to first-line immunotherapy and improved substantially on Rituximab.

CASE PRESENTATION PATIENT 1

A 35-year-old previously healthy male presented to the Emergency Room (ER) of Aga Khan University Hospital with complaints of agitation, decreased appetite, and irrelevant talk for three months. Over this period the patient had been quick to anger, and verbally abusive for two months, which was followed by one month of hallucinations, delusions, and social withdrawal. This included episodes of locking his children into a room since voices would tell him that they were in danger. One week before presenting to the ER, the patient was diagnosed with bipolar disorder at a psychiatry clinic and was given one mg of Risperidone to be taken twice a day. However, the treatment was not effective, and his condition worsened over the next week at which point he was brought to the ER.

On examination, his vitals were stable with a blood pressure of 124/85mm Hg, heart rate of 74/min, respiratory rate of 16/min, and a temperature of 37°C. The general physical examination was unremarkable. On neurological examination, the patient was alert but confused, not oriented to time or place, and could only

follow one-step commands. Cranial nerves and motor examination were unremarkable. There were no signs of meningeal irritation while the cerebellum and sensory system could not be assessed due to a lack of cooperation from the patient. A complete blood count and an electrolyte panel done on admission were normal. Workup for Wilson disease and urine toxicology screen was also unremarkable. Over the last day of admission, the patient became encephalopathic and was moved from the psychiatry service to the neurology service where an MRI Brain with contrast and Lumbar Puncture (LP) for CSF- analysis were performed which showed no abnormalities (Figure I).

Multiple EEGs over the course of the five-day hospitalization showed no changes. A serum autoimmune encephalitis workup was also sent. The patient improved to an MRS of 0 over the course of five days and was discharged with a diagnosis of bipolar disorder on Lamotrigine 25 mg once daily and Quetiapine 12.5 mg twice daily. The patient presented to the ER three days later with drowsiness, fever, and one episode of eye up rolling and frothing which was not associated with jerking movements of the body, incontinence, or tongue biting. The patient was readmitted to the neurology service. A repeat MRI Brain, EEG, and CSF analysis was done which showed no changes. Meanwhile, the patient's serum autoimmune encephalitis workup came back weakly positive for anti- NMDA receptor antibody. A workup was then sent for paraneoplastic antibodies along with a CSF sample for autoimmune encephalitis. The paraneoplastic antibody work-up was borderline positive for SOX1 antibodies. A CT scan of the chest, abdomen, pelvis, and tumor markers for liver, prostate, and testicular tumors were sent. The CSF sample was strongly positive for anti-NMDA antibodies.

The patient commenced on a pulse dose of intravenous methylprednisolone (1000 mg once daily for five days) along with a five-day course of IVIG. The patient did not improve over the course of treatment and was then started on Rituximab one day after his course of methylprednisolone and IVIG finished. After the first dose of Rituximab, the patient had an improvement in his consciousness level and was soon able to follow one-step commands and move all four limbs spontaneously. The patient has since undergone a four-week treatment with Rituximab and has been doing well at two months of follow-up. No treatment-related complications were experienced by the patient.

CASE PRESENTATION PATIENT 2

A 41-year-old previously healthy male presented to the ER of Aga Khan University Hospital with complaints of forgetfulness for two months and changes in behavior for the last 15 days. Over the past two months the patient, who was a radiologist by profession, started forgetting medical terminology. The patient visited a neurology clinic where MRI and EEG were both reported as unremarkable and so, he was referred to a psychiatrist who prescribed Vortioxetine (20mg once daily) Alprazolam (0.5mg once daily), and Propranolol (20mg twice daily). This treatment did not help, and the memory loss progressed to not being able to recognize distant and sometimes close relatives. Additionally, over the past 15 days, the patient developed irrelevant speech, restlessness, and repetition of words which worsened acutely over the 24 hours before the patient was brought to the ER.

At this point his blood pressure was 118/67 mm Hg, pulse was 70 beats/min and regular, respiratory rate was 16/min and the temperature was 37°C. A general physical examination showed no abnormalities. On neurological examination, the patient was alert, persevering in speech, and could only follow one-step commands. A mini-mental state examination showed a score of 11/30. The cranial nerve exam and motor exam were unremarkable. There were no signs of meningeal irritation. The cerebellar and sensory system examination was compromised due to the inability of the patient to comprehend instructions.

MRI Brain with contrast was unremarkable for any abnormality as shown in Figure 2. Serum infective, metabolic, paraneoplastic, and autoimmune workup showed no abnormalities. CSF analysis and cultures were also negative. However, both serum and CSF samples tested positive for anti-NMDA receptor antibodies. CT scan of the chest, abdomen, and pelvis showed no visible tumors.

The patient was started on methylprednisolone and improved on the second dose of treatment and was able to follow commands. On the third day, however, the patient became drowsy again after which the decision to start Rituximab was taken. The patient improved rapidly on Rituximab to an MMSE score of 22/30 and was discharged after two doses of Rituximab had been given under observation. Post third dose, the patient became aggressive and hypersexual with multiple incidents of public masturbation for which the psychiatry service was consulted, and he was diagnosed with steroid-induced psychosis. This improved with treatment with haloperidol. The patient has since received the fourth dose of Rituximab as well. On follow-up, he no longer repeats words, has an improved memory and his speech is more understandable. There were no complications reported by the patient after receiving rituximab.

Table 1 demonstrates details of investigations of both patients.

TABLE I: INVESTIGATIONAL DETAILS OF CASE 1 AND CASE 2		
Variants	Case 1	Case 2
Age/ Gender	35 / Male	41/ Male
MRI Brain	Unremarkable	Unremarkable
CSF Studies	Unremarkable	Unremarkable
Autoimmune Workup	NMDA +++	NMDA ++
Paraneoplastic panel	SOX-1 +	negative
Rituximab doses	4	3
Follow-up Visit	Improved	improve

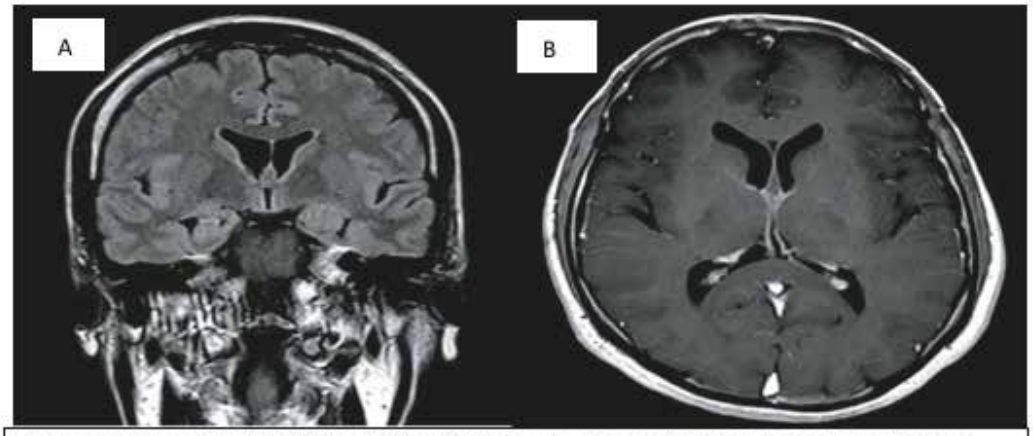

Figure 1: MRI brain FLAIR (a) and T1-weighted contrast image (b) showing no hyperintensity, edema, or leptomeningeal enhancement.

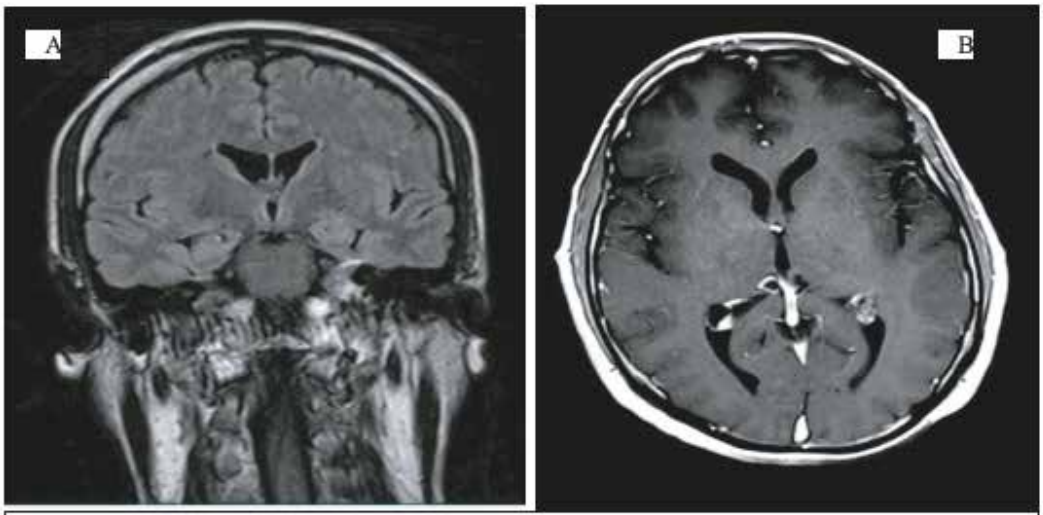

Figure 2: MRI FLAIR (a) coronal cut, and MRI brain (b) axial cut with contrast showing no hyperintensity, edema, or leptomeningeal enhancement.

DISCUSSION

Since the initial description of anti-NMDAR encephalitis in 2007, an increasing number of cases have been identified.[4,7] Many cases previously classified as encephalitis of unknown etiology are now recognized within this spectrum. However, owing to limited access to specialized laboratories capable of testing for anti-NMDAR antibodies and the relatively recent recognition of the disease, reports from Pakistan remain scarce and are largely confined to case reports.[9,10] Consequently, diagnosis is often delayed, as patients are frequently misdiagnosed with primary psychiatric disorders, as observed in both of our cases. In both patients, testing for anti-NMDAR antibodies was performed more than two months after the onset of psychiatric symptoms.

We describe our experience with early rituximab therapy in patients with anti-NMDAR encephalitis. Both patients experienced several months of progressive symptoms, initially presenting prominent psychiatric manifestations that resulted in misdiagnosis and treatment delay. At the time of diagnosis, both had impaired consciousness and showed no response to first-line immunotherapy. Clinical improvement followed rituximab administration, although one patient subsequently developed aggression and hypersexuality.

Early diagnosis and timely initiation of treatment are associated with favorable recovery outcomes. Patients who fail to respond to first-line therapies—such as corticosteroids, intravenous immunoglobulin, or plasmapheresis—often show significant improvement with second-line immunotherapies, including cyclophosphamide or rituximab.[11] In patients with associated tumors, these treatments are combined with surgical tumor resection. Notably, a substantial proportion of patients, particularly those without identifiable tumors, do not respond to first-line therapy but demonstrate favorable outcomes following second-line immunotherapy.[6]

Patients treated with rituximab tend to achieve functional independence earlier.[12,13] Shin et al. proposed rituximab as a first-line therapeutic option, with expert consensus supporting an aggressive treatment strategy combining corticosteroids, intravenous immunoglobulin or plasmapheresis, and rituximab to modify the course of this potentially fatal disease.[14] This approach is increasingly favored due to rituximab's demonstrated role in reducing relapse rates.[13,15] Furthermore, continuation of monthly rituximab therapy beyond the initial four weeks has been associated with improved outcomes.[16]

Despite this, practice patterns vary globally. In a survey by Bartolini et al., physicians in the United States were more likely to initiate second-line immunotherapy, most commonly rituximab, earlier than their international counterparts; however, rituximab was still largely classified as a second-line agent across regions. Notably, only 10% of respondents reported using rituximab as first-line therapy.[17] Additionally, a meta-analysis by Nosadini et al. demonstrated a temporal increase in the use of rituximab as second-line immunotherapy, accompanied by a corresponding decline in relapse rates over time.[12]

CONCLUSION

Currently, there are no standardized guidelines defining the optimal use of second-line immunosuppressive therapies. However, available evidence identifies rituximab as the most commonly utilized immunotherapy, with consistently favorable clinical outcomes. We propose that early initiation of rituximab may positively influence disease progression and should be considered in patients with anti-NMDAR encephalitis.

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Salman Farooq; concept, manuscript writing
Shafaq Saleem; case management, manuscript writing
Mohammad Bilal Tariq; case management, manuscript writing

All the authors have approved the final version of the article and agree to be accountable for all aspects of the work.