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Available online at: http://www.iajps.com *A Case Report*

IS RITUXIMAB AN EFFECTIVE TREATMENT FOR REFRACTORY ANTI-NMDA RECEPTOR ENCEPHALITIS?

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Abstract:

:Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune disorder in which antibodies target NR1/NR2 heteromers of the NMDA receptor in the brain (Ishiura et al., 2008). It is characterized by severe psychiatric and neurological symptoms such as memory loss, seizures, decreased consciousness, autonomic dysregulation, and dyskinesias (Kuppuswamy, Takala, & Sola, 2014). Most commonly affecting young females, and frequently associated with ovarian teratoma (Ishiura et al., 2008). The diagnosis is confirmed by the presence of antibodies in CSF (Kayser & Dalmau, 2016). The definitive treatment of anti-NMDA receptor encephalitis still remains unclear (Ishiura et al., 2008). This case report of a patient with anti-NMDA receptor encephalitis presented with schizophrenic psychosis and status epilepticus illustrating a complete recovery to baseline in two weeks after aggressive treatment of rituximab infusion.

Keywords: *AntiNMDA, Status Epilepticus , Seizure , Encephalitis, Psychosis, Catatonia*

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CASE REPORT:

A 25-year-old lady medically free, had a history of a new onset two seizures that were 48 hours apart. On admission, her seizures recurred and became refractory, she has ten brief seizures recorded per day, clinical and subclinical. With deterioration of her seizure, she started to have neuropsychiatric manifestations in the form of visual and auditory hallucination, progressed over days to the level of psychosis. She became awake unaware in majority of days. Seizures were refractory to anti-epileptic drugs. Brain Magnetic resonance imaging (MRI) with and without contrast were unremarkable. An Initial interictal (EEG) demonstrated a rare left temporal epileptiform discharges, frequent bilateral frontotemporal slow activity (left > right) and Intermittent generalized slow activity (Figure 1). The patient was started loading and maintenance dose of Levetiracetam and empirically on Acyclovir (10 mg/kg IV).

She started to get agitated, with visual and auditory hallucinations on day 3. She presented with different seizure semiology based on International League Against Epilepsy ILAE she presented with the following, orofacial lingual dyskinesia, focal aware motor onset seizure (automatism :orofacial), focal impaired awareness non motor onset (cognitive), focal impaired awareness non motor onset (emotional), focal impaired awareness non motor onset (behavior arrest), and focal to bilateral tonic-clonic. Also, she had a catatonic schizophrenia based of DSM5 Catatonia criteria, in the form stupor, catalepsy, waxy flexibility, mutism, stereotypy, echolalia, echopraxia, which is significant to diagnose catatonic schizophrenia.

Olanzapine was initiated but she became more agitated and having aggressive behaviour. Therefore, olanzapine dose was increased plus haloperidol when necessary. Cerebrospinal fluid (CSF) appeared clear and colourless fluid, WBC (49 10^6/L, reference range: 0-5), RBC (0 10^6/L, reference range: 0-0), Lymphocyte (93%), Monocyte (7%), Glucose (3.29 mmol/L, reference range: 2.20 – 3.90), Serum blood sugar (5.8 mmol/L, reference range: 3.9 - 7.1 mmol/L), Protein (197 mg/L, reference range: 150 – 450), Gram stain and culture, and HSV PCR were negative. antinuclear antibody (ANA), Anti-Sjögren's-syndrome type A antigen (Anti SSA), Anti-Sjögren-syndrome type B antigen (Anti SSB), Anti cardiolipin, Anti b2 glycoprotein, Antiphospholipid antibodies and Complements were all within normal limit. Long-term video-electroencephalography (EEG) demonstrated a seizure arising from posterior head region on/off lasted 10-40 seconds, semicontinous asymmetry over right hemisphere max right temporal (slow rhythmic delta and occasional periodic delta like PDA) (Figure 2). A positron emission tomography (PET) scan showed a diffuse asymmetrical hypometabolism noted involving the left fronto-parieto-occipito-temporal lobes as well as right occipital lobe and right cerebellum. There is mild asymmetrical reduce metabolic activity noted in the left basal ganglia and thalamus compared to the right side. worrisome for encephalitis (Figure 4). Ultrasonography (US) ovaries and Chest-abdomen-pelvis computed tomography (CT CAP) were unremarkable. Levetiracetam was stopped due to agitation. Valproic acid (500 mg) started on day 4, which was stopped after few days due to high ammonia level.

On day 5 she was started on methylprednisolone (1g IV) and IVIG (0.4 g/kg) completed 5 days, she started to improve only for 2 days and then deteriorated. She started to have frequent episodes of incoherent speech, recurrent left head and eye deviation lasted less than 15 seconds, followed by postictal confusion. On day 8, Lamictal (25 mg) started gradually then stopped due to skin rash. Paraneoplastic panel returned to be normal. EEG showed seizure evolved right hemisphere (Figure 3).

Day 14, plasma exchange was started with mild iprovement after five sessions in terms of seizure but not psychosis. Rituximab was initiated on day 19 for two sessions two weeks apart which showed dramatic improvement after the first dose where she has not had psychosis or seizures. The second dose was given on day 33, which result in a virtually complete recovery to baseline. On day 23, autoimmune panel came back positive for NMDA antibody from CSF. The patient was discharged on day 37 with complete recovery. She was following up monthly in refractory epilepsy clinic and her medications were tapered off gradually until she stopped them completely after nine months with no seizures.

DISCUSSION:

Multiple therapeutic treatments were given to our patient, however, the only effective treatment achieved with rituximab that showed dramatic improvement leading to complete recovery from psychosis and seizures.

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis treatment is determined by the presence or absence of the tumour. The initial management includes corticosteroids, IVIG, or plasmapheresis. Approximately 80% show beneficial response to tumour removal and first-line immunotherapy,

however, the initial response rate is 48% of the first-line immunotherapy in the absence of tumour. Rituximab and/or cyclophosphamide are considered a second-line therapy (Dalmau, Lancaster, Martinez-Hernandez, Rosenfeld, & Balice-Gordon, 2011). The mechanism of action of Rituximab is unknown, however, it plays a major role in an antibody-mediated disease by targeting anti-CD20 resulting in reduction of B-cells maturation into antibody-secreting cells and subsequent depletion of antibody-producing B-cells. Therefore, rituximab plays a critical role in anti-NMDA receptor encephalitis (Hallowell, Tebedge, Oates, & Hand, 2017). We are unaware of similar cases in adult with Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis that responded dramatically to rituximab infusions showing a complete recovery to baseline within two weeks in adult. However, one case has been reported in the literature with language deficits in paediatric age group that showed marked improvement of her speech within two days of the initial rituximab infusion, and almost complete recovery to baseline after two weeks prior to the second infusion of rituximab (Hallowell et al., 2017).

CONCLUSION:

this case illustrates the importance of considering Rituximab in patients who fail the first line immunotherapy in the absence of tumour which plays a major role in achieving complete recovery and minimizing the sequelae.

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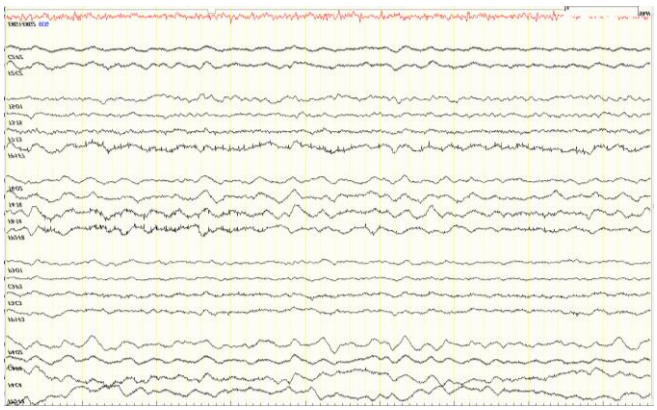

Figure 1:

Bipolar montages: Background of 6 Hz, low to moderate voltage, poorly sustained and asymmetric. And continuous to semi continuous asymmetry over the right hemisphere 3-4 Hz, moderate voltage (right hemisphere slower than left). Delta was of 2-3 Hz, low to medium voltage, arrhythmic, moderately persistent, diffuse, moderate to large amount. Continuous over the right hemisphere.

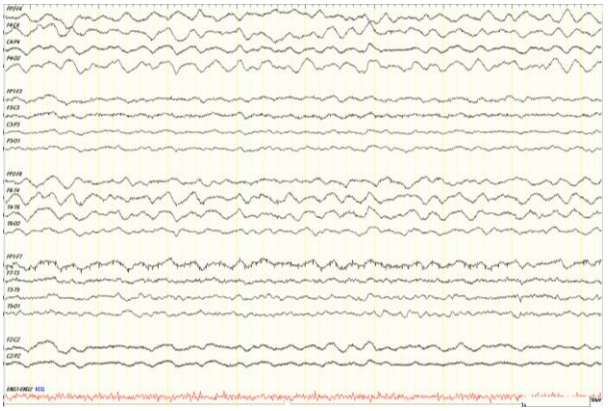

Figure 2:

A posterior rhythm is seen are maximum of 6 Hz, poorly maintained, asymmetrical. Clinical and electrographic seizure semiology were all similar EEG onset multiple recorded and it showed restless , behavioral arrest ,oral automatism sometimes with head deviation to the left. Electrographically were arising from the right hemisphere (in form of periodic delta activity) (PDA) FP2-F4 ,P4, occasionally seen also at F4-C4 and F8-T6. 2-3 Hz, lasting of approximately 2 minutes , started at F4-

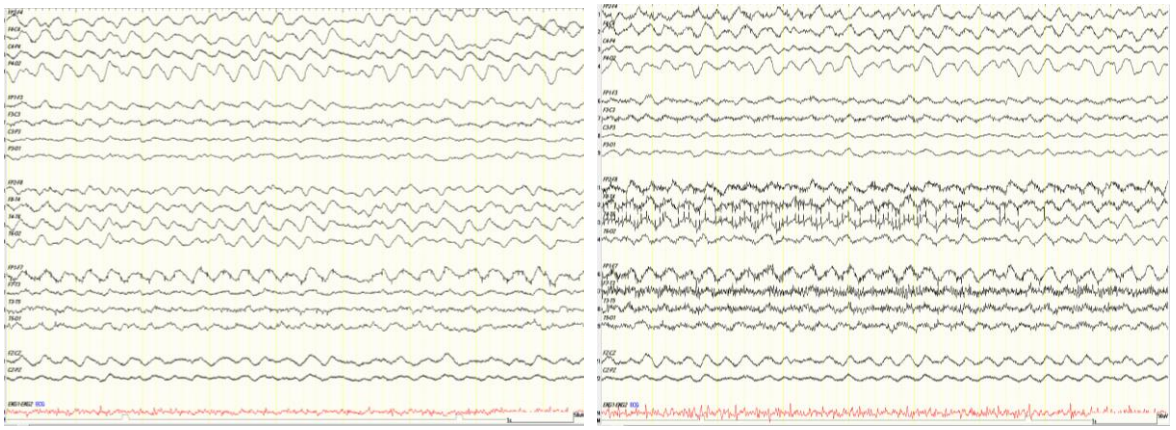

Figure 3:

Seizure evolved right hemisphere

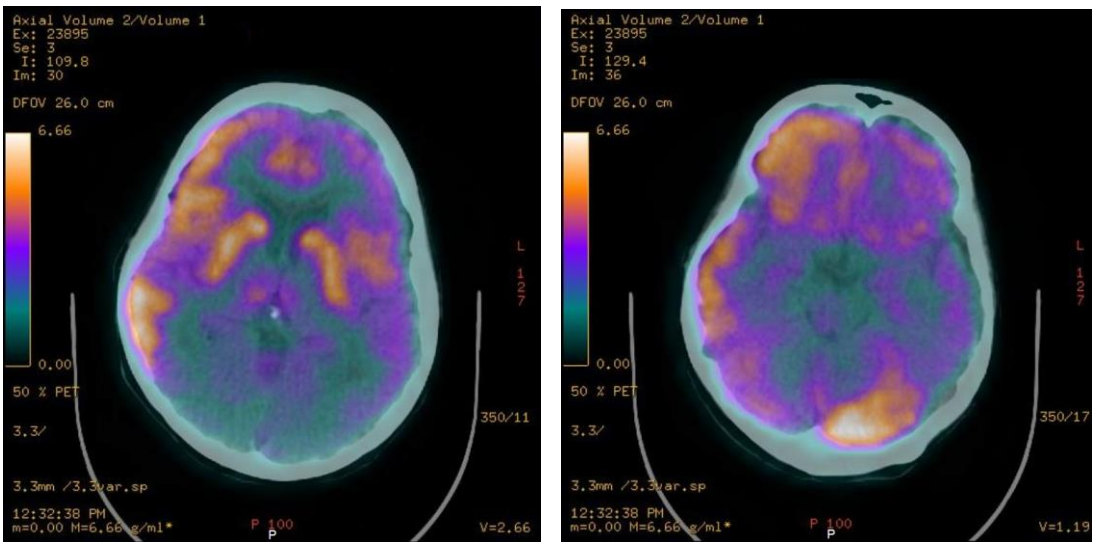
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Figure 4: