

Case Study

A CASE SERIES ON ANTI NMDAR ENCEPHALITIS

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ABSTRACT

N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune neurological disorder arising from the generation of antibodies which binds to the synaptic proteins. Here we present a case series of 3 cases where the different aspects of treating NMDAR encephalitis are dealt with. The association of ovarian teratoma and the importance of its removal before treating the encephalitis have been discussed in the second case. Apart from the first line and second line agents used in the therapy of NMDAR encephalitis, the importance of managing infections especially urinary tract infection and lower respiratory tract infection with antibiotics have also been discussed. The article also aims to throw light into the treatment of extrapyramidal side effects induced by antipsychotics. At the end, the significance of putting the patient on a ketogenic diet to manage refractory seizures associated with anti-NMDA receptor encephalitis has also been discussed based on reviewing literature.

Keywords: NMDAR Encephalitis, Synaptic proteins, Ovarian teratoma, Extrapyramidal side effects, Ketogenic diet

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INTRODUCTION

N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune neurological disorder arising from the generation of antibodies which binds to the synaptic proteins. It was initially classified as a paraneoplastic syndrome [1] due to the strong association with a teratoma (ovarian teratoma) or another tumor type. Usually, 80% of the sufferers are females [2] and are under the age of 19 [3]. In anti-NMDA receptor encephalitis, antibodies are against the NR1 subunit of the receptor. Clinical manifestations include a typical prodromal phase which shows non specific symptoms, psychotic phase, unresponsive phase with catalepsy like symptoms, hyperkinetic phase with orofacial limb dyskinesias and finally recovery phase. Serum antibodies can provide a useful marker for monitoring disease activity. While the confirmation of ovarian teratoma or any other possible sites of malignancy can be done using Fluorine-18 Fluorodeoxyglucose Positron emission tomography-computed tomography (18F FDG PET/CT) imaging under electroencephalogram (EEG) monitoring [4]. Corticosteroids, immunoglobulin or plasmapheresis can be used as first line agents. Second line agents like rituximab, a B-cell depleting monoclonal antibody, and/or cyclophosphamide, an alkylating agent (that interferes with DNA transcription), should be used in case the patient is not responding to first-line agents.

CASE REPORT

CASE 1

A female child, aged 10 y, came to our hospital with a seizure episode. She was undergoing treatment with antipsychotics in the previous hospital where she was admitted as she had presented there with psychiatric symptoms. Several investigations were done in our hospital. MRI was normal. Since EEG showed abnormalities, she was initiated on tab valparin (sodium valproate) 200 mg b. d (twice daily) and her antipsychotics were also continued while awaiting for the neuroimmunology reports. The results showed NMDA type of glutamate receptor antibody positive in cerebrospinal fluid (CSF) and negative in serum. She was diagnosed with anti NMDAR encephalitis in Sept 2015. She was given one course of intravenous immunoglobulin (IV Ig) and corticosteroids during this period and was discharged with advice to review in neurology OPD.

The patient was admitted again on 15 Jan 2016 with complaints of back pain and difficulty in writing. She was diagnosed with drug induced hepatitis during this admission. After stopping tab valparin

(sodium valproate), the liver function test (LFT) showed falling trend. She was discharged with tab clonazepam 0.25 mg b. d, tab carnisure (L-Carnitine) 330 mg b. d, tab. pan(pantoprazole) 20 mg 1-0-0 and tab udiliv (ursodeoxycholic acid) 300 mg b. d.

She was admitted again on 27 Feb 2016 for break through seizures and initiated on tab levipil (levetiracetam) 250 mg ½-0-1. LFTs were found to be normal during this time.

She was admitted for the fourth time on 15 March 2016 for aggression, behavioural outbursts and her parents sought to stop levipil in view of behavioural changes. Levipil dose was decreased. In this admission also a neuroimmunology study was sent. This time the patient's CSF and Serum samples tested positive for NMDA type of glutamate receptor antibody. She was given pulse methylprednisolone for 5 d. Her discharge medications included tab. levipil 250 mg 1/2-0-1/2 tab. wysolone (prednisolone) 30 mg 1-0-0 tab. olanzapine 2.5 mg 1/2-0-1, tab clonazepam 0.25 mg b. d, tab. serenace (haloperidol) 0.5 mg b. d She was advised IV Ig. It was not given due to financial constraints. The option of plasmapheresis was also discussed with parents, and the patient was discharged. She was given IV Ig from a Government hospital, 10 gm for 5 d and 5 gm on 6th day (total 55 gm).

She was admitted for the fifth time as her clinical symptoms progressed to akinetic mute state with dystonia of left upper limb, walking with support and fluctuation in symptoms (catatonic features). Based on history and physical examination, the child was considered to have a fluctuating behavior secondary to the natural course of disease with extrapyramidal signs probably secondary to antipsychotics. Routine lab evaluation was normal except for deranged LFT and elevated creatine phosphokinase (CPK). Psychiatric consultation was given, and it was advised to stop haloperidol and she was started on phenergan (promethazine) and clonazepam. EEG was done which showed a moderate degree of non-specific disturbance of electrical function over the right hemisphere. She was loaded with inj phenobarbitone and her steroid dose was hiked. Later repeat EEG showed a moderate degree of generalized non-specific disturbance of electrical function maximum over the right hemisphere. As the child continued to have recurrent seizures with behavioural changes despite treatment with IV methylprednisolone in the previous admission and IV Ig one week prior to the present admission, second line immunosuppressive agents were considered. Before rituximab infusion, CD 19 enumeration count was done. It was found to be within normal

limits and was asked to repeat the test after 6 w. She was given rituximab, 600 mg in 500 ml normal saline as per protocol on 19 April 2016 and 4 May 2016 under intensive care unit (ICU) care with strict monitoring of vitals. The child showed improvement in behaviour. During the hospital stay, child had an intermittent low-grade fever with dysuria. She was evaluated and was found to have urinary tract infection (UTI). She was managed with culture sensitive antibiotics. The second dose of rituximab was given after her urine culture and sensitivity showed no growth.

CASE 2

A female child, aged 17 y, came to our hospital with generalised tonic-clonic seizures. Earlier she was admitted in a government hospital for seizure, headache and fever. She was treated with mepresso (methylprednisolone) 1g o. d (once daily), esticef (ceftriaxone and sulbactam) 1.5g b. d, encorate (sodium valproate) 500 mg t. i. d, rabicon (rabeprazole) 20 mg o. d and her condition improved. Later on irrelevant talking and aggressiveness along with visual hallucinations occurred. So she has admitted again in a local hospital and was started with antipsychotics. She showed no significant improvement. MRI was normal. Abdominal and pelvic ultrasonography were done and showed mature ovarian teratoma and hence ovarian salpingoophorectomy was done. Again she developed fever, visual hallucinations and one episode of seizure. So she was readmitted in our hospital. She was given tab. encorate (sodium valproate) 500 mg 1-0-1, inj. levipil (levetiracetam) 500 mg 1-1-1, tab. quetiapine 25 mg 1-0-2 and inj. ceftriaxone 1g 1-0-1 (empirical therapy). Since her liver enzymes were found to be elevated (SGOT- 117.8 IU/l and SGPT- 152.4 IU/l), she was prescribed tab. udiliv (ursodeoxy cholic acid) 300 mg 1-0-1. Neuroimmunology results showed CSF NMDA type of glutamate receptor antibody and serum NMDA antibody positive but negative for leucine-rich glioma inactivated 1 (LGI-1) antibodies, voltage-gated potassium channel (VGKC) antibodies and contactin-associated protein-like 2 (CASPR2) antibodies by immunofluorescence on transfected cells. She was diagnosed with anti NMDAR encephalitis in march 2016 and was given first cycle IV Ig (60g) and inj. solumedrol (methylprednisolone) 1 g. Tab. encorate was stopped as the liver function tests continued to remain abnormal. Then, tab clonazepam 0.25 mg 1-1-1, tab. bromocriptine 5 mg t. i. d, tab. pacitane (trihexyphenidyl) 2 mg t. i. d, mucomix nebulisation (acetylcysteine) b. d, syp. ambrolite (ambroxol) 5 ml t. i. d were given. Her temperature increased (103 °F), both respiratory rate (12 breaths/min) and BP reduced (103/66 mmHg). Ecchymosis was present due to the administration of prednisolone. For that supportive treatment was given. Urine culture report showed the presence of *E. coli* (700cfu/ml) and hence she was prescribed inj. cefaperazone and sulbactam 2g 1-0-1. Again her liver enzymes elevated (SGOT-139.4 IU/l and SGPT-181.2 IU/l) and she had catatonic features. Since she was not responding to first-line agents (IV Ig and prednisolone), second line agent rituximab (500mg) was initiated. Tab. clonazepam was stopped because she was resistant to it and she was allergic to haloperidol. Tab. phenergan (promethazine) 25 mg 1-1-1 was given. Her temperature reduced (98 °F), BP became normal (127/90 mmHg), eye contact occurred and she tried to talk. Heparin was given as prophylaxis for deep vein thrombosis. Her condition improved. Her liver enzymes became 25.6 IU/l (SGOT) and 34 IU/l (SGPT). The patient was given 4 doses of rituximab and 2 doses of inj. cyclophosphamide according to infusion protocol with strict infection control. Cataleptic symptoms reduced. She responded to the commands and tried to wake up. The plan was to discharge the patient and admit for physiotherapy for active rehabilitation.

CASE 3

A girl child, aged 7 y, born out of non consanguineous marriage at term gestation by natural vaginal delivery. The child was developmentally normal till 5 y of age when she developed fever, altered sensorium and involuntary movements. She was diagnosed to have anti-NMDAR Encephalitis in April 2014. She was hospitalized for about three months. She was treated with IV Ig, pulse methylprednisolone, rituximab, antiepileptic drugs and pacitane (trihexyphenidyl). Tracheostomy was done and was sent home with NG (nasogastric) feeds.

The child was readmitted after 3 mo with complaints of fever and coughs and was treated as lower respiratory tract infection. Sputum culture and endotracheal suction culture done in the hospital showed *Proteus vulgaris*. She was treated with piptaz (piperacillin/tazobactam) as per culture and sensitivity reports. Repeat endotracheal suction culture was sterile.

The child was again admitted after 1 w with a cough and fever. The endotracheal suction culture showed *Pseudomonas* and was treated with multiple IV antibiotics (meropenem, colistin and piptaz). Her tracheostomy tube was changed during this admission. She was started on mycophenolate mofetil which was discontinued by the mother after two weeks.

We took up the case when the child was admitted in Dec 2014 during which she presented with intermittent fever of two weeks duration. She was on the following drugs when she was admitted: tab pacitane (trihexyphenidyl) 2 mg ½-0-1, tab clonazepam 0.25 mg 1-0-1, syp levipil (levetiracetam) (100 mg/ml) 5 ml b. d, tab shelcal (Calcium carbonate and vitamin d3) 500 mg ½ o. d, syp zincovit (multivitamin and mineral supplement) 5 ml o. d, syp gardenal (phenobarbital) (20 mg/5 ml) 5 ml h. s (at bedtime) and tab pan (pantoprazole) 20 mg 1-0-0. At the time of admission, the child was febrile, drowsy, glasgow coma scale (GCS) 6/15 with dystonic posturing and involuntary movements. Saturation was 94% with 1litre oxygen. Initial arterial blood gas (ABG) showed metabolic acidosis (pH: 7.284, pCO₂: 29.4, HCO₃:13.5). She had a serum creatinine of 2.52 mg/dl and markedly elevated liver enzymes (SGOT: 5493 IU/l, SGPT: 1716 IU/l). She was started on IV antibiotics, piptaz (piperacillin/tazobactam) and ofloxacin as per the culture sensitivity reports from outside and fluconazole were added.

Paediatric nephrology consultation was taken, and lasix (furosemide) was started along with maintenance IV fluids. As she developed hypotension lasix infusion was stopped and was started on ionotropic supports (dopamine, dobutamine). Serial renal function test (RFT) monitoring showed worsening trend (creatinine: 4.01 mg/dl, urea: 177.2 mg/dl). So peritoneal dialysis was initiated and was given for 48 h after which serial RFT monitoring showed improving trend. Peritoneal dialysis was stopped and was continued on lasix infusion which was gradually tapered and stopped. Pediatric neurology consultation was availed and was advised to stop phenobarbitone. The tracheostomy tube was changed on 23 Dec 2014.

As she continued to have high-grade fever spikes and bronchoalveolar lavage cultures showed growth of *Pseudomonas*, IV piptaz (piperacillin/tazobactam) was changed to inj meropenem and colistin nebulisation as per the culture sensitivity report. It was given for 10 d. Her RFT and LFT showed significant improvement. The child was discharged on NG feeds.

DISCUSSION

Anti NMDAR Encephalitis presents with a typical prodrome (fever, fatigue, headache, nausea and diarrhea), followed days later by the onset of psychiatric symptoms (hallucinations, mood lability, agitation, insomnia and delusional thought content). In the progression phase, most patients experience sleep disturbances, seizures, dyskinesias and alternating periods of agitation and catatonia followed by autonomic instability (tachycardia, bradycardia, central hypoventilation, hypotension and hyperthermia) [3]. In the first case, the patient was brought to the hospital, with complaints of temper tantrums, anger outbursts and aggression (noted over 1-2 w) and an episode of seizures.

She had an abnormal feeling of tightness of fingers of left hand and staring episodes. In the second case, the patient was brought to the hospital, with complaints of fever, headache, visual hallucinations, irrelevant speech, and abnormal behavior. In her progression phase, she had experienced insomnia, seizures, dyskinesias tremulousness of lower limb and alternating periods of agitation and autonomic instability characterized by tachycardia, bradycardia, central hypoventilation, hypotension and hyperthermia. In the third case, the child was admitted in the hospital with complaints of fever, altered sensorium and involuntary movements.

Diagnosis is made by clinical features, CSF pleocytosis, and antibodies to NMDA receptor in serum or CSF and diffuse delta activity with paroxysmal discharge in EEG [5]. MRI brain fluid-attenuated inversion recovery (FLAIR) pattern at presentation may be normal, or it may demonstrate bilateral or medial temporal lobe hyperintense signals mainly involving regions of the hippocampus [6]. NMDA type of glutamate receptor antibody was found in all the three patients CSF and serum. In the first case, EEG monitoring showed a moderate degree of focal nonspecific disturbance of electrical function maximum over the right hemisphere. MRI brain showed normal study. USG scan revealed no ovarian teratoma. In the second case MRI brain showed multifocal right parietal and occipital cortical T2 FLAIR hyperintensity which shows mild hyperintense signal on diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) sequence. Since the patient had mature ovarian teratoma, she underwent left ovarian salpingo-oophorectomy. In the third case, MRI showed subtle hyperintense lesion in the bilateral temporal lobe. EEG showed a moderate degree of nonspecific disturbance of electrical function. USG screening revealed no underlying neoplasm.

Under definitive treatment, we have surgical removal of the tumour, if identified and immunotherapy. In immunotherapy, a combination of corticosteroids and IV Ig or plasmapheresis can be given as first-line agent and rituximab or cyclophosphamide can be given as second-line agent [7]. In the first case, the patient was treated with pulse inj IV methylprednisolone 900 mg and IV Ig. Since the patient was unresponsive to first line agent, she was started on second-line agent as per protocol. The dose of rituximab given was 600 mg in 500 ml normal saline IV. In the second case, the patient was given intravenous immunoglobulin's (60g) and methylprednisolone (IVIg) as first-line therapy. Since the patient did not respond to first-line treatment, she was started on second-line agent rituximab (500 mg) and the patient was found to be gradually improving. In the third case, the patient was treated with second-line agents as she did not respond to first-line agents. There was no delay in providing treatment, but she suffered from lower respiratory tract infections due to tracheostomy.

CONCLUSION

In the first case, there was a delay in providing treatment as the symptoms of the patient was misunderstood as those related to the psychiatric condition. Even after the correct diagnosis was made, there was a lapse in providing adequate treatment due to financial constraints. Later on the child was efficiently managed with second-line agent. The child also exhibited extrapyramidal side effects due to long-term intake of anti-psychoics. The child had one episode of UTI. The second dose of immunosuppressant was given after the UTI resolved.

In the second case also no autoimmune encephalitis oriented treatment was given until post ovarian salpingo-oophorectomy. Then first line and second line agents were given. The extrapyramidal side effects caused by antipsychotics were managed by tab pacitane and tab bromocriptine. The second child also had only one episode of UTI. She also had steroid induced ecchymosis which was managed by ice application.

The third case had slightly different clinical outcomes despite early treatment with the first line and second line agents. Long-term use

of antipsychotics led to tardive dyskinesia and orofacial dyskinesia [8]. It was managed by tracheostomy. The patient was sent home on nasogastric feeds. As a consequence of which lower respiratory tract infection occurred. This was managed using antibiotics.

Periodic screening to rule out any underlying neoplasm should be done in all anti-NMDA receptor encephalitis patients. There have been several reports emphasizing the importance of ketogenic diet in the treatment of refractory seizures associated with anti-NMDA receptor encephalitis [9]. The preventable side effects of ketogenic diet include dyslipidemia, acidosis and kidney stones [10]. So prompt intervention and a culmination of all treatment plans including first line agents, second line agents, managing infection and putting the patient on a ketogenic diet are important for curing NMDAR encephalitis.

CONFLICT OF INTERESTS

Declared none

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