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. 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.

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 catatlep like symptoms, hyperkineatic 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 carnitine (L-Carnitine) 330 mg b. d, tab panpantoprazole 20 mg 1-0-0 and tab udvid (ursodeoxycholic acid) 300 mg b. d.

She was admitted again on 27 Feb 2016 for break through seizures and initiated on tab levetiracetam (kevitraacetam) 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 levetir in view of behavioural changes. Levetir 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 levet 250 mg 1/2-0-1/2, tab wysolone (prednisolone) 30 mg 1-0-0, tab clonazapine 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. EGG 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. After stopping the infusion, she was discharged with tab mycophenolate mofetil 250 mg b. d and inj rituximab 1 g IV infusion bolus over 4 h. She was discharged on 15 April 2016.
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 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 piperacillin/tazobactam). 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, syrup leviracetam (levetracetam) 500 mg b. d, tab shekal (Calcium carbonate and vitamin d3) 500 mg ½ 0. d, syrup chinoin (multivitamin and mineral supplement) 5 ml 0. d, syp genalin (phenobarbital) (20 mg/5 ml) 5 ml h. s (at bedtime) and tab pan (panoprole) 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 1 litre oxygen. Initial arterial blood gases (ABG) showed metabolic acidosis (pH: 7.284, pO2: 294, 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, piperacillin/tazobactam and olloasin 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, her lasix infusion was stopped and was started on ionotopic 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 tapering and stopped. Paediatric neurology consultation was availed and was advised to stop phenobarbital. 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 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 diarrhoea), 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 hyperventilation, 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 hyperventilation, hypotension and hyperthermia [3]. In the third case, the child was admitted in the hospital with complaints of fever, altered sensorium and involuntary movements.

**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 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. 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

REFERENCES


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