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Clinical Profile and Long Term Outcome of NMDA Receptor Encephalitis- A Tertiary Care Centre Experience

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Abstract
Introduction: *Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune encephalitis which predominantly affects children and young adults especially females.*
Aim: *To study the clinical profile and long term outcome of the patients with Anti NMDA receptor antibody positive encephalitis and assess their response to treatment.*
Materials and Methods: *Patients admitted in our ward or ICU satisfying the criteria of possible autoimmune encephalitis with a cerebrospinal fluid NMDA Positivity were included. Data including the clinical features, cerebrospinal fluid findings, MRI brain findings, electroencephalography findings and treatment received was noted. All the patients had undergone screening for tumours especially ovarian teratoma. [USG/CT ABDOMEN/MRI ABDOMEN] .Follow up was done at six months and improvement was assessed at follow up.*
Results: *Mean age of our patients was 16 years and 91.7% of patients were females. Most common symptoms were behaviour changes and seizures.50 percentage of our patients went to a psychiatrist for initial consultation. CSF pleocytosis was seen in 83% of patients. MRI Brain was normal in 58 % of patients. EEG slowing was seen in all patients. We could detect ovarian teratoma in 27.3% of female patients. Only two patients improved with steroids alone. Rest other patients required second line immunotherapy and rituximab. Majority of patients in our study improved without much sequel.*
Conclusion: *So a young female with new onset of behavioural symptoms, possibility of Autoimmune encephalitis should always be considered and investigated. Early identification and early initiation of treatment shows better response*
Keyword: *Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis.*

Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune encephalitis known after 2007[1,2]. An UK study showed that among all case of encephalitis 4% of patients had anti-NMDAR encephalitis[3]. Antibodies against the NR1 subunit of the NMDAR (NMDAR antibodies) produces this characteristic syndrome which affects children and young adults especially females.

Aim of our study was to study the clinical profile and long term outcome of the patients with Anti NMDA receptor antibody positive encephalitis and assess their response to treatment.

Methods

Our study was a descriptive study which was conducted in department of Neurology, Government Medical College, Thiruvanantha-puram after getting the approval from the human ethics committee .Patients admitted in our ward or ICU satisfying the criteria of possible autoimmune encephalitis with a Cerebrospinal fluid NMDA Positivity were included from January 2014 to January 2016(4).All other causes of encephalitis (like viral encephalitis) and encephalopathy were excluded.

Data including the clinical features, cerebrospinal fluid findings, MRI brain findings, electroencephalography (EEG) findings and treatment received was noted. Assay for anti NMDAR antibody was done using cell based assays.All the patients had undergone screening for tumours especially ovarian teratoma. [USG/CT ABDOMEN/MRI ABDOMEN].

Follow up was also recorded. Improvement was assessed with the modified Rankin scale (MRS)[(5)]. Patients will be labelled as having full recovery if they could go back to their normal life and job (MRS 0, normal cognition). Mild deficits was defined if they couldreturn to most activities of daily living and remained stable (MRS 1–2; mild cognitive dysfunction).Rest other cases were taken as severe deficits. Improvement was also assessed based on reduction in seizure frequency. Good Response was defined as reduction in seizure frequency to more than or equal to 50% of admission. Poor Response was defined as reduction in seizure frequency to less than 50% of admission. Improvement was also assessed based on symptom [extrapyramidal/speech disturbances] improvement[(6)].

Results

Twelve patients satisfied the criteria of autoimmune encephalitis with positive CSF anti NMDAR antibody. Mean age of presentation was 16 years. Majority of the patients were females (91.7%,11 patients).

Most common symptoms were behaviour changes (91.67%) and seizures (83.3%).

Table 1- Symptoms of NMDARE

Symptoms	No of patients	Percentage (%)
Behaviour changes	11	91.67
Seizures	10	83.3
Fever at onset	9	75
Extrapyramidal	7	58.3
Decreased speech or language disturbance	2	16.7
Headache	2	16.7

Half the patients initially consulted a psychiatrist.

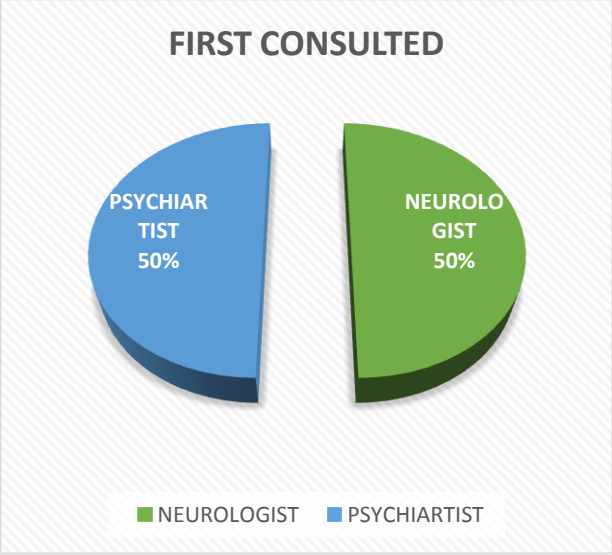

Figure 1 Pie diagram showed distribution of patient's first consultation

Most common Cerebrospinal fluid findings were lymphocytic pleocytosis (83.3%) and increased protein (66.7%).CSF was normal in two patients.

Table 2 Cerebrospinal fluid findings

CSF Findings	Number of patients	Percentage (%)
CSF normal	2	16.7
CSF Lymphocytic pleocytosis	10	83.3
CSF protein elevated	8	66.7

MRI Brain was done in all patients. MRI was normal in seven patients (58.3%).

Table 3 imaging findings

MRI Brain finding	Number of patients	Percentage (%)
Normal	7	58.3
Frontal T2W hyperintensities	2	16.7
Occipital T2W hyperintensities	2	16.7
Mesial temporal T2W hyperintensities	1	8.3

Electroencephalography (EEG) was abnormal in all patients. Background slowing was the most common findings. Inter epileptiform discharges were seen in frontal and occipital region in six patients.

Table 3 Electroencephalography (EEG) findings

EEG Findings	Number of patients	Percentage (%)
Generalised slowing(delta 1 generalised)	8	66.7
Generalised slowing(delta 2 generalised)	4	33.3
Frontal inter epileptiform discharges	3	25
Occipital inter epileptiform discharges	3	25
Delta brush	2	16.7

Imaging for malignancy was done in all patients. Patients underwent MRI or CT abdomen, pelvis and thorax. Ovarian teratoma was detected in three out of eleven (27.3 %) patients. Male patient did not have any malignancy.

All patients received one gram of methyl prednisolone intravenous for 5 days initially. In case of lack of improvement in one week, we started plasma exchange (2.5 litre of plasma per exchange for 5 exchanges) or Intravenous immunoglobulin followed by rituximab injection (500 mg IV injection 4 injections, one week apart).

Table 4- treatment given

Treatment given	No of patients	Percentage (%)
Methyl prednisolone IV	12	100
Plasma exchange	10	83.3
Rituximab	8	66.7
Intravenous immunoglobulin	1	8.3
Teratoma surgery	3	25

All patients completed six month follow up. Regarding seizure control, all patients showed good response. Two patients who had language dysfunction improved completely. Mild Cognitive dysfunction (episodic memory) persisted in two patient.

Table 5- 6 month outcome of treatment

Outcome at 6 months	No of patients	Percentage (%)
Full recovery	10	83.3
Mild deficits	2	16.7
severe deficits	0	0

Discussion

Mean age of our patients was 16 years which was slightly younger when compared to other studies. Josep Dalmau et al. study showed a mean age of 23 years[1]. 91.7% of patients were females which was similar with other studies[1,7] Most common symptoms were behaviour changes and seizures which was also similar to other studies[1,7].

50 percentages of our patients went to a psychiatrist for initial consultation. In similar studies, 77% went for a psychiatry consultation first[1]. CSF pleocytosis was seen in 83% of patients when compared with other studies where it was seen in 91%[1]. Pleocytosis was of lymphocytic predominant type.MRI Brain was normal in 58 % of patients. Other studies showed a normal MRI in 33%[7] and 50 %. Normal MRI in an encephalitic patient cannot be used to rule out NMDAR encephalitis[8].

EEG slowing was seen in all patients. In other studies, 71 %[1] and 90%[7] patients showed EEG slowing. We could detect ovarian teratoma in 27.3% of female patients which is lesser than other studies[1]. Only two patients improved with steroids alone. Rest other patients required second line immunotherapy and rituximab. This is comparable to other studies where 92% were treated with first-line immunotherapy (steroid and Plasmapheresis/IVIg) and 27% with second-line immunotherapy (Rituximab)[7]. Majority of patients in our study improved without much sequel. In in other studies, 85% patients were left with mild deficits[1] and 78% patients achieved a good outcome[7].

Conclusion

Anti-NMDAR encephalitis must be suspected in young patients with encephalitic syndrome with prominent neuro psychiatric symptoms and seizures. Early aggressive immunotherapy must be started in such a scenario. Tumour screening must be done in all patients.Early identification and early initiation of treatment shows better response

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