CHARACTERISTICS AND OUTCOMES IN PATIENTS WITH ANTI N-METHYL-D-ASPARTATE RECEPTOR AUTO-IMMUNE ENCEPHALITIS

Syed Onaiz Zulfiqar Anwar, Jahanzeb Liaqat*, Waseem Alamgir*

Combined Military Hospital Multan Pakistan, *Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

Objective: To study characteristics and outcome in patients with anti-N-Methyl-D-Aspartic Receptor encephalitis.
Study Design: Retrospective observational cohort.
Place and Duration of Study: Neurology Department Military Hospital Rawalpindi, from Feb 2015 to Sep 2016.
Material and Methods: Data of patients admitted with anti-n-methyl-D-aspartate receptor encephalitis was analyzed retrospectively. Patients were classified as having definite or probable anti-N-methyl-D-sspartate receptor encephalitis whether antibody testing in CSF was positive or negative respectively and fulfillment of other defined parameters. Patient characteristics, treatment protocols and outcomes were noted.
Results: Eleven patients were included in this cohort. Six (54.5%) were males and 5 (45.5%) were female. Mean age was 31.18 years (SD 14.865). Mean day to symptom onset was 18.51 days (SD 16.646). Abnormal behavior was seen in 90.9%, Seizures and movement disorder in 81.8%, speech dysfunction in 72.7%, decreased level of consciousness in 63.6% and autonomic dysfunction in 54.5% anti-N-methyl-D-aspartate receptor antibodies were done in CSF in 3 patients only out of which 2 were positive. In remaining nine patients antibody testing was not done due non availability of facility and or affordability. Out of eleven patients 2 (18.25%) had definite encephalitis and 7 (81.8%) had probable encephalitis. CSF was abnormal in 63.6% with pleocytosis in 18.2% and oligoclonal bands in 45.5%. EEG was abnormal in 72.7% and MRI was annormal in 36.4%. Outcome was favorable in 63.6% and unfavorable in 36.4%.
Conclusion: In this study we were able to determine that patients with anti-N-Methyl-D-Aspartate Receptor encephalitis have a favorable outcome if diagnosed and treated aggressively early in the course of disease.

Keywords: Anti-n-methyl-D-aspartate, Cerebrospinal fluid, Cyclophosphamide, Electro-encephalogram, IV immunoglobulin, Plasma exchange.

INTRODUCTION

N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis was described in 2007[1] for the very first time and is now taken as one of the leading causes of Autoimmune Encephalitis[2]. Anti-NMDAR encephalitis is a multi-stage disease with nonspecific prodromal flu-like symptoms including fever and cough followed by psychiatric manifestations such as psychosis, delusions, hallucinations, anxiety etc. Patients at this stage generally present to psychiatry services. This is followed by altered level of consciousness with periods of agitation and catatonia. This is usually accompanied with classical orofacial and lingual dyskinesias, autonomic instability, focal and generalized seizures. This results in referral to a Neurology setup. Anti-NMDAR encephalitis is usually associated with ovarian teratomas, especially in females older than 12 years. 67% of the patients have abnormal MRI Brain studies. EEG can be abnormal in 90% of patients[3]. The diagnosis is confirmed by the presence of NMDAR antibodies in the CSF. Treatment consists of multi-prong therapy with immune suppression and tumor removal, when present. Generally, first-line immunotherapies for this condition consist of high-dose steroids, IV immunoglobulin (IVIg), and plasma exchange (PE). Different setups use these treatments alone, in combination, or sequentially. Data is lacking in establishing superiority of any specific therapy. Primary selection depends more upon personal experiences and response to specific therapiy. Rituximab and cyclophosphamide are usually

Correspondence: Dr Syed Onaiz Zulfiqar Anwar, Neurologist, CMH Multan Pakistan (*Email: onaiz24@gmail.com*)
Received: 23 Jan 2017; revised received: 09 Feb 2017; accepted: 02 Mar 2017

considered second-line treatments, and reserved for those patients who fail the first line or develop a relapse.

The rationale of this study was to raise awareness of a potentially treatable life threatening neurological emergency. Despite growing interest in auto-immune encephalitis, this area is still poorly understood.

MATERIAL AND METHODS

We retrospectively analyzed data of eleven cases of definite and probable NMDAR encephalitis admitted to neurology department of military hospital, Rawalpindi from February 2015 to September 2016 for a total duration of one year and 10 months. Permission from hospital ethical committee was obtained prior to start of the study. A total of eleven patients were included (criteria given below) who were classified as having definite or probable NMDAR encephalitis whether antibody testing in CSF were positive or negative respectively and fulfillment of other clinical parameters[17].

Diagnosis can be made when all three of the following criteria have been met:

Rapid onset (less than 3 months) of at least four of the six following major groups of symptoms

- Abnormal behavior or cognitive dysfunction.
- Speech dysfunction.
- Seizures.
- Movement disorder, or rigidity.
- Altered level of consciousness.
- Autonomic dysfunction.

At least one of the following laboratory study results

- Abnormal EEG (focal or diffuse slow activity, epileptic activity, or delta brush).
- CSF with pleocytosis or oligoclonal bands.

Reasonable exclusion of other disorders

- Diagnosis can also be made in the presence of three of the above groups of symptoms accompanied by a systemic teratoma.
- Diagnosis was made in the presence symptoms and IgG NMDAR antibodies.

In all patients extensive workup was done to exclude other autoimmune, vasculitic and infectious diseases. All patients were given methylprednisolone along with either plasma exchange or intravenous immunoglobulins as first line therapy, Non responders were given cyclophosphamide and rituximab was given as second line therapy depending upon response to first line therapy and persisting severity of symptoms.

Data Analysis

Data was noted on a Patient Particular proforma and descriptive analysis of data was performed using SPSS version 21. Categorical variables were expressed as percentages and quantitative variables were expressed as mean.

RESULTS

A total of eleven patients were studied in this cohort. Out of the 6 (54.5%) were males and 5 (45.5%) were female. Mean age was 31.18 years. (SD 14.865). Mean day to symptom onset was 18.51 days (SD 16.646). Patient characteristics are shown in table-I.

In speech dysfunction, mutism was seen in 63.6%, decreased verbal 27.3% and ecolalia in 9.1%. In movement disorder, rigidity was seen in 54.5% and orofacial dyskinesia in 36.4%. CSF was abnormal in 63.6% with pleocytosis in 18.2% and oligoclonal bands in 45.5%. EEG was abnormal in 72.7% of patients and MRI Brain was abnormal in 36.4%. Medial temporal hyper intensities were seen in 27.3% and subcortical in 9.1%. Anti NMDAR antibodies were tested in CSF, only in 3 (27.25) patients, 2 (81.2%) were positive and 1 (18.2%) were negative. In 8 (72.7%) patients antibody testing was not done due non-availability of facility/affordability. Out of eleven patients 2 (18.25%) had definite NMDAR encephalitis and 7 (81.8%) had probable NMDAR encephalitis.

All patients were given methylprednisolone initially. Definite cases were given IVIgs along

with methylprednisolone. PE was done either with methylprednisolone or after pulse therapy. Non-responders were given cyclophosphamide either alone or in combination with rituximab (table-II).

Single case of definite anti-NMDAR encephalitis died because of cardiac arrest secondary to severe autonomic dysfunction. Two cases of probable anti-NMDAR encephalitis received only methylprednisolone and developed refractory status epilepticus leading to death. One patient of probable anti-NMDAR encephalitis died because of severe sepsis (table-III).

Table-I: Characteristic features of Anti-N-Methyl-D-Aspartate auto-immune encephalitis.

S. No	Patient characteristic	Percentage (%)
1	Abnormal behavior	90.9
2	Seizures	81.8
3	Movement disorder	81.8
4	Speech dysfunction	72.7
5	Decreased level of consciousness	63.6
6	Autonomic dysfunction	54.5

Table-II: Treatment modalities used in Anti-N-Methyl-D-Aspartate auto-immune encephalitis.

S. No	Treatment mortality	Percentage (%)
1	Methylprednisolone	100
2	Plasma exchange	36.4
3	Intravenous immunoglobulins	45.5
4	Cyclophosphamide	81.8
5	Rituximab	18.2
6	Cyclophosphamide + rituximab	18.2

Table-III: Outcome of patients in anti-N-Methyl-D-Aspartate receptor auto-immune encphalitis.

Outcome	No of cases	Definite	Probable	Percentage (%)
Favorable	7	1	6	63.6
Unfavorable	4	1	3	36.4

DISCUSSION

Encephalitis is a severe inflammatory disorder of the brain with many causes and complexity in differential diagnosis[4]. The most frequent cause of encephalitis is still infectious[5,6] however in the past 10 years, autoimmune encephalitis cases have been identified and advances in encephalitis research have led to the identification of different clinical syndromes related to auto-immunity. These new forms of encephalitis might be associated with neuronal cell-surface antibodies or synaptic proteins antibodies and can develop symptoms resembling infectious encephalitis, other neurological and psychiatric manifestations without even fever or CSF pleocytosis[7].

A research published in 2010 suggests that anti-NMDA receptor encephalitis is the most common cause of autoimmune encephalitis[8]. Anti-NMDA receptor encephalitis is recognizable on clinical grounds and is associated with CSF IgG antibodies against NMDA receptors[9]. NMDA receptor antibodies block NMDA receptor in the presynaptic gamma-aminobutyric acid (GABA)-ergic neurons of different parts of the brain including thalamus, frontal cortex and limbic system, leading to a disinhibition of postsynaptic glutamatergic and dopaminergic neurons leading to functional dysregulation primarily in the frontal, temporal cortex and basal ganglia. The prominent psychotic symptoms of catatonia and orofacial dyskinesias show dopaminergic involvement. Patients usually have abnormal behaviour (psychosis, delusions, hallucinations, agitation, aggression) with irritability and insomnia, followed by speech dysfunction, dyskinesias, memory deficits, autonomic instability,

and alteration in the level of consciousness[10]. Seizures either focal or gener-alized can take place at any time during the course of illness.

In another multicenter, observational study where 577 patients were studied, most of the patients had similar clinical picture in initial 3-4 weeks. 498 (87%) of 571 patients developed four or more of the symptoms, mentioned previously with additional central hypoventilation and cerebellar ataxia or hemiparesis[11].

In our study, abnormal behavior was seen 90.9% followed by seizures 81.8% which were focal with evolution into bilateral convulsive seizures. Two patients developed refractory status epilepticus requiring general anesthesia. Movement disorders were seen in 81.7%. Rigidity was most common 54.5% and orofacial dyskinesias in 36.4%. Catatonic presentation with generalized rigidity mimicking neuroleptic malignant syndrome was seen in two patients. Speech dysfunction was seen in 72.7% with mutism (63.6%) being most common followed by decreased verbal communication (27.3%) and echolalia (9%). Decreased level of consciousness was seen in 63.6% and autonomic manifestation in 54.5% leading to cardiac arrest in one patient.

We considered patient with rapidly progressing cerebral dysfunction and having fulfilled 4 out of these 6 symptoms complex as having probable anti-NMDA receptor encephalitis. These patients under went extensive workup to rule out other diseases having similar presentation. In addition, the search for a neoplasm (according to sex and age) was also done with CT scan Chest, Abdomen and pelvis.

In another retrospective observational cohort study of 3425 patients, 254 (74%) of 342 had teratoma and 171 (90%) of 189 had no teratoma[11]. None of our patients had any underlying malignancy.

CSF abnormalities is seen in approximately 80% of cases, and can show increased protein concentration, lymphocytic pleocytosis or oligoc-lonal bands[11,12]. We found CSF abnormality in 63.7% with pleocytosis in 18.2% and oligoclonal bands in 45.5%.

MRI brain scans were reported normal in 70% of cases[3], in the remainder, hyperintensities in different regions of the brain were evident (hippocampi, cerebellar and cerebral cortex, basal ganglia, brainstem, frontobasal and insular regions)[13]. Our findings are similar with abnormal MRI in 36.4%, medial temporal hyper intensities were seen in 27.3% and subcortical in 9.1%. Electroencephalograms (EEGs) was abnormal in 72.7% of our cases and is very helpful if one is trying to distinguish between encephalitis and a primary psychiatric disorder, as the majority of patients (90%) with anti-NMDA receptor encephalitis have evidence of non-specific slowing, extreme delta brush, epileptic or disorganized activity[14].

Treatment protocols consist of immuno-suppression, tumor removal and supportive therapy. Generally, first-line immuno-therapies for this condition consist of high-dose steroids, IV immunoglobulin (IVIg), and plasma exchange (PE). Different setups use these treatments alone, in combination, or sequentially. Data is lacking in establishing superiority of any specific therapy. Plasma exchange was done in 36.4% of our patients and 45.5% were treated with IVIgs. There are no data to support that PE is superior to IVIg. From an immunological perspective, the anti-bodies related to this disorder are synthesized both systemically and in the brain. PE can remove them systemically but cannot alter the autoimmune process inside the brain. This is the reason that up to 14% of patients do not have serum antibodies but have positive CSF antibodies[15]. Also, it can be very challenging to do it in patients with autonomic instability and extreme agitation. So, generally IVIg treatment is usually considered at the outset. The response to first-line treatment is usually evaluated clinically after 10-15 days. In more than half of the patients who fail to respond to first line get benefit from second-line immunotherapy. Rituximab and cyclophosphamide are usually considered second-line treatments, and reserved

for those patients who fail the first line. Rituximab is given for at a dose of 375 mg/m^2 every week for 4 weeks. Cyclophosphamide is given every 2 weeks in the dose of 750 mg/m^2 for 4-6 months (an alkylating agent that interferes with DNA replication and eliminates T regulatory cells), especially in adults. These treatments are given alone or in combination, depending upon the clinical symptoms and response to first line therapy.

All of our patients received second line immunotherapy. Cyclophosphamide was given in 81.8% and rituximab in 18.2%. Two patients with definite anti-NMDAR encephalitis received dual immunotherapy with combination of cyclophosphamide and rituximab, If a patient had a relapse, we usually considered repeating the same treatment that had helped initially, or giving a second-line agent if it was not given previously. We currently do not use mycophenolate and azathioprine. In fact, there are no studies to show that these drugs are effective in the acute stage or are useful to prevent relapses. We definitely need multicenter prospective studies to evaluate the efficacy of all these immunotherapies.

Outcome was favorable in 63.6% of patients which signifies a very good prognosis if treated early and aggressive.

CONCLUSION

Anti-NMDA receptor encephalitis is a relatively new disease entity and a treatable cause of neuro-psychiatric symptoms in both adults and children. It is clear that early identification and treatment may have prognostic implications on disability. Delay to treatment with immune-suppressive therapy probably results in worsened outcomes, with evidence for permanent hippocampal damage[16] or even death. It is vital for clinicians and psychiatrists to be aware of this condition and engage in timely liaison with their neurology colleagues, thus facilitating early screening and diagnosis.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

REFERENCES

1. Dalmau J, Tüzün E, Wu HY, Masjuan J, Rossi JE, Voloschin A, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encepha-litis associated with ovarian teratoma. Ann Neurol 2007; 61(1): 25-36.
2. Gable MS, Sheriff H, Dalmau J, Tilley DH, Glaser CA. The frequency of autoimmune N-methyl-Daspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California Encephalitis Project. Clin Infect Dis 2012; 54(7): 899-904.
3. Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 2013; 12(2): 157-65.
4. Venkatesan A, Tunkel AR, Bloch KC, Lauring AS, Sejvar J, Bitnun A, et al. Case defi nitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. Clin Infect Dis 2013; 57(8): 1114-28.
5. Ball R, Halsey N, Braun MM, Moulton LH, Gale AD, Rammohan K, et al. Development of case definitions for acute encepha-lopathy, encephalitis, and multiple sclerosis reports to the vaccine: Adverse Event Reporting System. J Clin Epidemiol 2002; 55(8): 819–24.
6. Britton PN, Eastwood K, Paterson B, Durrheim DN, Dale RC, Cheng AC, et al. Consensus guidelines for the investigation and management of encephalitis in adults and children in Australia and New Zealand. Intern Med J 2015; 45(5): 563-76.
7. Leypoldt F, Armangue T, Dalmau J. Autoimmune enceph-alopathies. Ann N Y Acad Sci 2015; 1338: 94-114.
8. Granerod J, Ambrose HE, Davies NW, Clewley JP,Walsh AL, Morgan D, et al. Causes of encephalitis and differences in their clinical presentations in England: A multicentre, population-based prospective study. Lancet Infect Dis 2010; 10(12): 835-44.
9. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investi-gations in patients with anti-NMDAR encephalitis. Lancet Neurol 2011; 10(1): 63–74.
10. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: Case series and analysis of the eff ects of antibodies. Lancet Neurol 2008; 7(12): 1091–98.
11. Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 2013; 12(2): 157–65.
12. Barry H, Hardiman O, Healy DG, Keogan M, Moroney J, Molnar PP, et al. Anti-NMDA receptor encephalitis: an important differential diagnosis in psychosis. Br J Psychiatry 2011; 199(6): 508-9.
13. Dalmau J, Tuzun E, Wu HY, Masjuan J, Rossi JE, Voloschin A, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 2007; 61(1): 25-36.
14. Florance NR, Davis RL, Lam C, Szperka C, Zhou L, Ahmad S, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol 2009; 66(1): 11-8.
15. Gresa-Arribas N, Titulaer MJ, Torrents A, Aguilar E, McCracken L, Leypoldt F, et al. Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: A retrospective study. Lancet Neurol 2014; 13(2): 167–77.
16. Finke C, Kopp UA, Pruss H, Dalmau J, Wandinger KP, Ploner CJ. Cognitive deficits following anti-NMDA receptor encephalitis. J Neurol Neurosurg Psychiatry 2012; 83(2): 195-8.
17. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol 2016; 15(4): 391-404.