CASE SERIES

Anti NMDA receptor antibody encephalitis in Pakistan: Clinicopathological features and treatment outcomes

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Abstract

Anti-NMDA receptor antibody encephalitis (anti-NMDAR Encephalitis) is the most common subtype of autoimmune encephalitis in which IgG antibodies directed against NR1 subunit of NMDA receptors are present. It is a potentially lethal encephalitis which responds favourably to timely immunosuppressive therapy. If untreated, its progression leads from delusions, paranoia, movement disorder, memory deficit and seizures into a state of unresponsiveness with autonomic instability and even death. We present clinicopathological features, treatment and outcomes of eight autoantibody-proven cases of anti-NMDAR Encephalitis. There were 7 females and 1 male with a mean age of 15 years (age range: 1 to 28 years). Clinical features included seizures, altered consciousness, memory deficit, delusions, paranoia and hallucinations. Hyperactivity and irritability were prominent features among the children. Patients treated with immunosuppressive therapy including steroids, IVIg, plasmapheresis and Rituximab, recovered completely within a month of therapy. Whereas patients who received only steroids as immunosuppressive therapy suffered from residual brain damage.

Keywords: Anti-NMDAR Encephalitis, Immunosuppressive therapy, plasmapheresis, IVIG.

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Introduction

Anti-NMDA receptor antibody encephalitis (anti NMDAR Encephalitis) is an autoimmune disease in which the body creates antibodies against the NMDA receptors present in brain. It is the most common subtype of autoimmune encephalitis and constitutes around 4% of all the causes of encephalitis.[1] It is also more common than most among the viral causes of encephalitis in the age group of less than 30 years. IgG antibodies directed against NR1 subunits of glutamate receptors are the diagnostic findings in this disease. Anti-NMDAR Encephalitis is considered to be relatively more prevalent among Asians and Africans, with approximately 500 cases reported to date.

Anti-NMDAR Encephalitis presents clinically with a prodrome of fever, nausea, vomiting, diarrhoea and upper respiratory tract symptoms, followed within a couple of weeks by psychiatric symptoms due to which many patients end up presenting in psychiatric clinics.[2] Psychiatric symptoms include bizarre behaviour, agitation, delusions, paranoia, visual and auditory hallucinations. Cognitive dysfunction is often reported comprising of short-term memory loss and difficulties in concentration. Seizures often progressing to epilepticus status are one of the most frequent initial manifestations. Movement disorder includes orofacial dyskinesias and chorea. Patients can also suffer from autonomic dysfunction and hypoventilation.

In children prominent clinical features include hyperactivity and behaviour changes including temper tantrums and irritability. According to Dalmau and colleagues, anti-NMDAR Encephalitis is often associated with an underlying neoplasm in 59% of patients.[3] However, children under the age of 18 are less likely to have an underlying tumour. The etiology of anti NMDA R Encephalitis is unknown but infections including Mycoplasma pneumonia, EBV and endogenous retroviruses can cause breakdown of self tolerance hence triggering autoimmunity.

The gold standard for diagnosing anti-NMDAR encephalitis is autoantibody testing in either serum or CSF. Timely diagnosis and prompt immunomodulating treatment can alter the course of this potentially lethal yet treatable cause of encephalitis. This study presents clinical features and treatment outcomes of eight patients with autoantibody-proven anti-NMDAR encephalitis with a view to facilitate accurate diagnosis and timely institution of recommended treatment.

Case Series

Ethical approval for this descriptive case series was taken from the Institutional Review Board of Shifa International Hospital / Shifa Tameer-e-Millat University, Islamabad. Informed consent for the

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Table-1: Clinical data, treatment and response of anti NMDAR Encephalitis patients: Cases 1 to 4.

	Case 1	Case 2	Case 3	Case 4
Age and Gender	5 year male	1 year female	6 female	26 year female
Prodrome	+	-	+	+
Seizures	+	+	+	+
Memory deficit	-	-	+	+
Altered consciousness	-	-	+	+
Delusions	-	-	-	+
Paranoia	-	-	-	+
hallucinations	-	-	-	+
Hyperactivity and irritability	+	+	+	-
Dyskinesias/chorera	-/-	-/-	-/-	+/+
Autonomic dysfunction	Urinary incontinence	Nil	Labile pulse and BP	Nil
Autoantibody Detection	In serum	Both serum and CSF	CSF Only	CSF Only
Other Tests	USG abdomen normal		USG abdomen normal	
Treatment	Inj solumedrol 500mg OD IVIG -5 days	InJ Solumedrol IVIG For 5 days	Injectable steroids for 21 days. Followed by oral steroids. 0.5ml/day to date.	Inj solumedrol 500 mg for 7 days
Response	Good; recovered within one month. No relapse after 15 months	Good; recovered within three weeks	Hearing and speech deficit (only babbles). Motor deficit improved after 8 months of physiotherapy.	Speech and motor deficit persists to date, after 7 months of follow up.

Key: OD :Once Daily, IVIG : Intravenous immunoglobulin, CSF :Cerebrospinal Fluid, USG:Ultrasonography.

Table-2: Clinical data, treatment and response of anti NMDAR Encephalitis patients: Cases 5 to 8.

	Case 5	Case 6	Case 7	Case 8
Age and Gender	27 year female	28 year female	6 year female	23 year female
Prodrome	+	-	+	-
Seizures	+	+	+	+
Memory deficit	+	+	-	-
Altered consciousness	+	-	+	+
Delusions	+	-	-	-
Paranoia	+	-	-	-
Hallucinations	-	-	-	-
Hyperactivity and irritability	+	+	-	-
Dyskinesias/Chorea	-/-	-/-	+/-	+/-
Autonomic dysfunction	Urinary incontinence	Hyperpyrexia	Nil	Nil
Autoantibody Detection	In serum	Both serum and CSF	CSF Only	CSF Only
Other Tests	USG and CT scan abdomen and pelvis normal	USG abdomen and pelvis-B/L ovarian teratomas	CSF: Predominant lymphocytosis. MRI head: focal hemorrhages in R temporal lobe, gliosis and brain tissue loss.	Predominant lymphocytosis in CSF. CT SCAN abdomen and pelvis: normal
Treatment	Inj MP 500mg OD-5 days IVIG -400mg/kg/day 5 days. Tab Deltacortil 1mg/kg/day	InJ MP 500mg OD-3 Days Plasmapheresis 5 sessions each followed by IVIG	Inj MP 250 mg -3days Decadron 1cc-2 days IVIG 30g total over 4 days. Azathioprine 50mg (1/4 tablet)-14 days	Inj MP 1g-3 days IVIg 2.8g/day for 5 days Rituximab
Response	Good ;recovered within one month.	Good; recovered within 2 weeks	Recovered in 1 week. Aggresiveness persists.	Good; recovered in 3 weeks.

Key: MP=Methyl prednisolone, IVIg=Intravenous Immunoglobulins, OD= once daily, USG:Ultrasonography, CT:Computed Tomography.

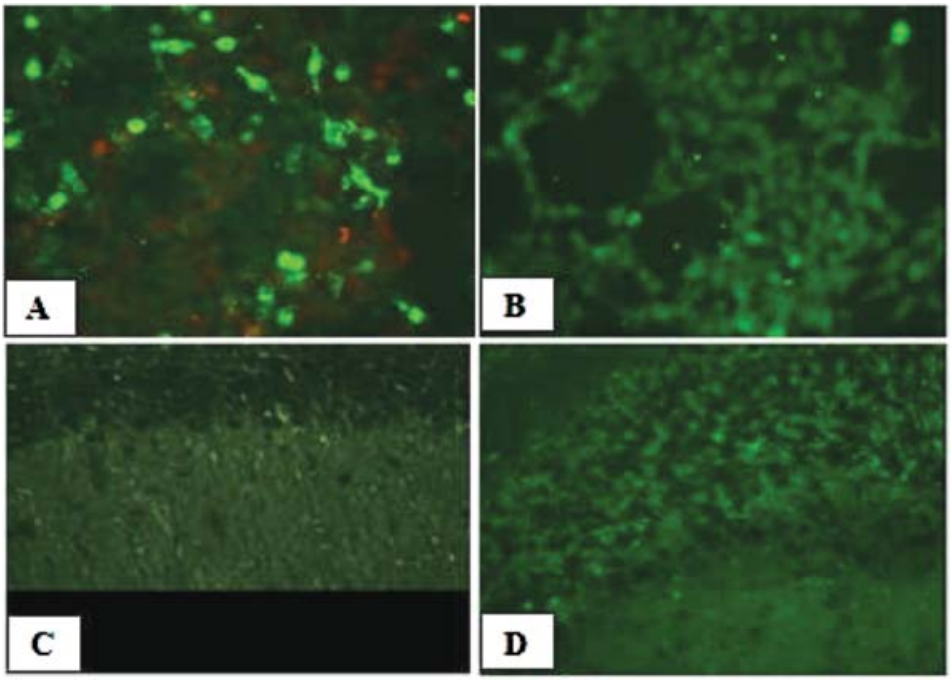

Figure-1: Photomicrograph showing, A. U90 cell line transfected with NMDAf gene, B. U90 cell line not transfected with NMDA with NMDAR gene, C. Rodent hippocampus sections and D. Rodent cerebellum sections after staining with one of the patient's serum POSITIVE anti-NMDA r antibodies.

A. U90 cell line transfected with NMDAr gene clearly showing bright granular positivity in cell cytoplasm on cell membrane with membrane showing characteristic protrusions.

B. Patient's serum with NMDAr antibodies on U90cells not transfected with NMDAr gene.

C. Rodent hippocampus section showing granular positivity with patient's serum positive for NMDAr antibodies in molecular layer.

D. Rodent cerebellum section showing nodular positivity in intercellular area in granular layer of cerebellum after staining with patient serum positive for antiNMDAr antibodies.

collection of relevant information was taken from patients' relatives. Clinical information was obtained by reviewing the patient's referral forms and discharge summary; interviewing the patient's primary caregiver and physician or interviewing patients themselves (after recovery), as illustrated in Tables-1 and 2. Samples for autoantibody testing were received in the laboratory of our own institution (Shifa International Hospital) as well as from other medical institutions. The data of patients who tested positive for the antibodies was collected within a period of fifteen months, from December 2016 to February 2018. Patients with clinical suspicion of autoimmune encephalitis who tested positive for antibodies of anti-NMDA receptor in serum or CSF were included in the study. Four anti-NMDA receptor antibody-positive patients were excluded as their required clinical information was not provided.

All specimens, including serum and CSF were tested for anti-NMDAR IgG antibodies by indirect immunofluorescence (IIF), using tissue sections of rat cerebellum, rat hippocampus and U 90 cells transfected with genes of the NR1 subunit of the NMDAR complex, that are fixed on slides (prepared by Euroimmun Luebeck Germany). Slides were incubated with serum samples (diluted at 1:10) or CSF samples (undiluted) for thirty minutes and then washed and stained with fluorescein-labeled anti-human IgG antibodies and analysed using a fluorescence microscope. Samples were classified as positive if they induced a characteristic staining in the molecular layer of rodent hippocampus (Figure-1C), or granular layer of rodent cerebellum (Figure-1D), along with a fine granular cytoplasmic and cell membrane florescence with typical cellular protrusions on the transfected U 90 cells (Figure-1A) compared to no staining in non-transfected cells (Figure-1B).

Results

Out of 267 specimens received that had clinical suspicion of autoimmune encephalitis within the specified time period, our data shows a 4% positivity with 12 patients who were found positive for anti-NMDAR antibodies. Patients included in the study were seven females and one male. The mean age was 15±10.9 years (age range: 1 to 28 years). A wide spectrum of clinical features was observed (Table-1 and 2) which included a prodrome of fever and flu-like illness in 5 patients, seizures in 8 patients, with seizures being the first symptom in 4, impaired consciousness in 5 patients, short-term memory loss in 4 patients, dyskinesias in 3 patients, delusions and paranoia in 2 patients, visual and auditory hallucinations in 1 patient and chorea in 1 patient. Four patients had shown autonomic instability featuring hyperpyrexia in 1 patient, labile BP and heart rate in 1 patient and urinary incontinence in 2 patients.

Treatment included immunotherapy with injection methyl prednisolone, Immune-globulins (IVIg), plasmapheresis, Rituximab and Azathioprine. Along with immunosuppressive therapy anti-epileptic drugs,

antiviral, antibiotics, antipsychotics, mood stabilisers were also administered in some patients depending on their symptoms. Three patients received a combination immunosuppressive therapy with steroids and IVIg. One patient received steroids, IVIg and plasmapheresis; 1 received steroids and IVIg followed by Azathioprine; 1 was treated with Steroids, IVIg and Rituximab and 2 received only steroids as immunosuppressive therapy. Patients who were treated only with steroids suffered from residual brain damage (Table-1). At the time of preparation of this manuscript, a follow-up was available for 4 patients over a period ranging from 7 to 12 months. The follow-ups revealed no relapse.

Discussion

In our study, 7 out of 8 patients were young females, which is consistent with the published data, according to which around 80% of the reported anti-NMDAR Encephalitis cases are females.[4] According to Dalmau and colleagues, prodromal period precedes clinical symptoms in around 70% of the patients.[5] Our study showed in 5 out of 8 patients, the onset was gradual starting with a viral-like prodrome progressing to seizures and altered consciousness. In addition, in one of our patients the onset was sudden, starting with seizures and progressing to loss of consciousness within a day (Case 8, Table-2). Psychiatric features were prominent in adults. In addition, in our study all younger patients, i.e., less than 7 years of age, suffered from hyperactivity and irritability (Cases 1, 2 and 3, Table-1).

Antibody studies are recommended to be carried out in both serum and CSF. CSF is more sensitive than serum for antibody detection and according to a recent study 14% of patients had antibodies in CSF only and not in serum.[6]

There are no published guidelines for treatment. First line of treatment includes methylprednisolone 1 g/day for 5 days followed by IVIg 0.4 g/kg/d for 5 days. All patients responded to first line immunosuppressive therapy which is consistent with findings of Titulaer et al who noted that 97% of patients have a good outcome at 24 months.[7] Two of our patients required a second line of immunotherapy. Recent data shows that more than half of the patients failed to respond to first line of immunotherapy and benefited from second-line of immunotherapy, consisting of Rituximab.[8]

According to Joseph Dalmau, Rituximab and both, Plasma Exchange and IVIg are used as part of the combination for immunosuppressive therapy at the University of Barcelona. It is yet unknown whether the combination of Plasma Exchange and IVIg is better than when either one of them is used alone.[8] In our study one patient underwent plasmapheresis along with IVIg and recovered earlier as opposed to those who only received steroids and IVIg.

In our study patients who were treated only with steroids as immunosuppressive therapy had poor outcome with residual brain damage, which is consistent with a previous study that concluded that the lack of specific immunosuppressive therapy will lead to permanent hippocampal damage.[9] According to an Indian case series study of 5 patients, 2 patients suffered mild residual brain damage in spite of receiving specific immunosuppressive therapy and 1 patient suffered a relapse.[10]

Conclusion

Anti-NMDAR Encephalitis should be suspected specifically in young females presenting with psychiatric symptoms with hyperactivity and irritability, followed by seizures and altered consciousness. Autoantibody testing and treatment initiation with specific immunosuppressive therapy should be undertaken promptly to prevent patients from permanent brain damage. Patients should be treated with a combination immunosuppressive therapy, including steroids, IVIg, Plasmapheresis or Rituximab.

Limitations

Drug dosage is not available in cases where information was taken from family members telephonically and where clinical charts were not available. Long term follow up was not available for some patients.

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References

1. Dalmau J, Graus F. Antibody-Mediated Encephalitis. N Engl J Med. 2018;378:840-51.
2. Barry H, Byrne S, Barrett E, Murphy KC, Cotter DR. Anti-N-methyl-d-aspartate receptor encephalitis: review of clinical presentation, diagnosis and treatment. Br J Psych Bull. 2015 ;39:19-23.
3. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, etal.Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 2008;7:1091-8
4. Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T,etal. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 2013;12:157-65.
5. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR,

Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. The Lancet Neurol. 2011;10:63-74.
6. Lee SK, Lee ST. The laboratory diagnosis of autoimmune encephalitis. J Epilepsy Res. 2016;6:45.
7. Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, Honig LS, Benseler SM, Kawachi I, Martinez-Hernandez E, Aguilar E. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 2013;12:157-65.
8. Bartolini L. Practice Current How do you treat anti-NMDA receptor encephalitis?. Neurology: Clin Pract. 2016;6:69-72.
9. Finke C, Kopp UA, Pajkert A, Behrens JR, Leypoldt F, Wuerfel JT, etal. Structural hippocampal damage following anti-N-methyl-D-aspartate receptor encephalitis. Biological psychiatry. 2016;79:727-34.
10. Goenka A, Jain V. Anti NMDA receptor encephalitis. Indian J Paediatr. 2016; 83:1032