



A Case of Anti-NMDAR Encephalitis Successfully Treated with Cyclophosphomide

Authors

Ka Kiat Chin¹, Chee Koon Low¹, Sapia Sapuan²

¹Department of Medicine, Hospital Serdang

²Consultant Neurologist, Neurology unit, Department of Medicine, Hospital Sungai Buloh

Corresponding Author

Dr Ka Kiat Chin

Email: kk.chin@hotmail.com

Abstract

Anti-N-Methyl D-Aspartate Receptor (NMDAR) Encephalitis is a rare immune related encephalitis. The definitive diagnosis of the disease would be detection of Anti NMDAR autoantibodies in CSF fluid. The treatment are usually consist of corticosteroids, IVIG or plasma exchange. However, our patient required alternative therapy of Cyclophosphomide due to slow response to first line treatment. She was able to achieve full recovery with no relapse on 1 year follow up. We would like to share our experience of treating Anti-NMDAR Encephalitis by using Cyclophosphamide as an alternative when the first line therapy has failed. More data will be required in the future to develop an updated guideline to treat this rare disease.

Keywords- Anti-NMDAR encephalitis, cyclophosphomide, Oro-Facial dyskinesia, psychosis, seizures.

Introduction

Anti N-Methyl- D- Aspartate receptor (NMDAR) encephalitis is an immune- related encephalitis that often difficult to identify in the initial stage. This disease has been predominantly described in young females with acute psychosis, dyskinesias, seizures or speech disorders. It is frequently associated with ovarian teratoma. Management outlines mainly consist of immunosuppressive therapy or tumor removal. Relapses of anti –NMDAR encephalitis are common.

Case Report

We would like to report a case of Anti N-methyl-D-aspartate Receptor (NMDAR) Encephalitis in

Hospital Sungai Buloh, who was treated with plasma exchange and cyclophosphomide.

A 31 year-old lady, presented to a private hospital with acute onset of fever, headache and auditory hallucination after she came back from a trip in Bangkok on Dec 2015. She also experienced seizure on the day of admission. She did not have any viral like illness prior to her presentation. MRI of the brain did not show any abnormality. Two days later she started to have orofacial dyskinesia and subsequently dyskinetic movements over both upper and lower limbs. A repeated MRI did not show any abnormality. Cerebral fluid analysis showed positive for anti NMDAR antibody in cerebral spinal fluid (CSF). Unfortunately the titre was not

available. CT of the thorax and abdomen did not reveal any evidence of tumor.

She was started on intravenous Methylprednisolone for 5 consecutive days, followed by Intravenous Immunoglobulin (IVIG). Her condition remained unchanged with persistent orofacial dyskinesia and she was only able to speak single words, and unable to recognize family members. On arrival to our center, she was restless with poor Glasgow Coma Score of 8/15. Both her upper and lower limbs were stiffed with persistent dyskinesia. She was started on a course of plasma exchange (6 cycles) within one month of her illness followed by intravenous cyclophosphamide. The frequency of orofacial and limbs dyskinesia were markedly reduced upon completion the plasma exchange and she was able to obey two steps commands. She was discharged after two month of hospitalization walking with assistant but with poor cognition (MMSE of 6/30).

A total of six cycles of intravenous cyclophosphamide was given and subsequently she was put on maintenance therapy with Azathioprine. Her cognitive function improve tremendously with the treatment and she was able to be wean off from her antiepileptic drugs after 6 months of treatment and she went back to her previous work as sales promoter one year after her initial presentation.

Hemoglobin	12.2g/L
Total white counts	23.3
Platelet	362
CSF- Glucose	3.6
CSG – Protein	0.34
CSF – Cell count	80, predominantly Lymphocytes
Antineuronal Antibodies	Negative
Anti NMDA Receptor (CSF)	Positive
Anti NMDA Receptor (Serum)	Negative

Discussion

NMDAR encephalitis is an auto immunecaused by immunoglobulin (Ig)G antibodies directed against the NR1 subunit of the NMDA glutamate receptor⁽¹⁾. In the case series reported, females are more common than male, with median age 18-38 years. Eldest patient reported was 84 years old. Among female patients presented with anti-NMDAR encephalitis 62% were found to have ovarian

teratoma while small cell and testicular teratoma was found in 22% of male patients.⁽²⁾ The association between malignancy and anti-NMDAR encephalitis suggests that antibodies formed against tumor cells expressing NMDR receptor.⁽²⁾

Detection of auto antibodies NMDAR in the CSF would be the laboratory test to establish the diagnosis. Recognising the clinical syndrome in the early stage of the disease is challenging. The characteristic syndrome evolves as most patients (70%) presented with fever, diarrhea, vomiting, headache in prodromal phase. Within the next two weeks, they will develop psychiatric symptoms such as hallucination, delusions, depression and subsequently progressed to seizures, abnormal movements, or memory deficits.⁽²⁾ In this case, our patient presented with fever, headache and psychotic features, and progresses to orofacial and limbs dyskinesia and seizures, should raised the diagnostic suspicion. Differential diagnosis includes viral or bacterial meningoencephalitis, brain malignancy, or autoimmune disease such as systemic lupus erythematosus. CT scan or MRI of the brain are usually normal in anti-NMDAR encephalitis, however they are useful to exclude other causes.

Until now, there was no randomized controlled trial on the treatment in anti-NMDAR encephalitis. Most studies recommended first line treatment with corticosteroids, then proceeds with IVIG or plasma exchange. Cyclophosphamide, Azathioprine or Rituximab were suggested as alternative treatment.⁽²⁾ In a case series of total 10 patients in one of the tertiary center in Malaysia, the patients were treated with corticosteroids, IVIG and plasma exchange. Only 2 patients achieved full recovery while 3 patients had substantial recovery, 4 had partial recovery and 1 mortality. No second line treatment mentioned in this case series.⁽³⁾ Our patient received corticosteroids, followed by IVIG and plasma exchange. She was started on cyclophosphamide after plasma exchange due to slow recovery. She was able to communicate coherently with improvement in cognitive function after cyclophosphamide.

An observational cohort study showed 53% of patients with anti-NMDAR encephalitis who underwent treatment with first line immunotherapy (steroids, intravenous immunoglobulin or plasmapheresis) improved within 4 weeks. The remaining group who failed first line therapy, 57% of the patient improved with second line treatment (rituximab or cyclophosphamide). It showed that most of the patient responded to immunotherapy.⁽⁴⁾ Relapses of anti-NMDAR encephalitis occur about 20 to 25%, and patient with tumor removal had fewer neurologic relapses.^(5,6) Azathioprine had been recommended as maintenance therapy 1 year post recovery to reduce relapses. The patient was screened for possibility of malignancy and it was negative. She was on Azathioprine as maintenance therapy.

Conclusion

In summary, recovery can be achieved in anti-NMDAR encephalitis with cyclophosphomide. We also suggest for continuous cancer surveillance during follow up due to high association of ovarian teratoma with anti-NMDAR encephalitis. Further guidelines on follow up would be needed.

Disclosure Statement

No conflict of interest declared.

References

1. Pollak T. A., Mc Cormack R et al. Prevalence of anti-N-methyl-d-aspartate (NMDA) receptor antibodies in patients with schizophrenia and related psychoses: a systematic review and meta-analysis. *Psychological Medicine* 2014; 44(12): 2475-2487.
2. Gregory S. Day, Sasha M. High, Bianca Cot, David F. Tang-Wai. Anti-NMDA-Receptor Encephalitis: Case Report and Literature Review of an Under-Recognized Condition. *J Gen Internal Medicine*. 2011; 26(7):811-816.
3. Suhailah Abdullah, Shen-Yang Lim, Khean Jin Goh, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis: A series of ten cases from a university hospital in Malaysia. *Neurology Asia* 2011;16(3):241-6
4. Rosenfeld M, Dalmau J. Anti-NMDA-Encephalitis and other synaptic autoimmune disorders. *Current Treatment Options in Neurology*. 2011; 13(3):324-332.
5. Titulaer MJ, McCracken L et al. Treatment and prognostic factors for long term outcome in patients with anti-NMDA encephalitis: an observational cohort study. *Lancet Neurology*. 2013;12(2):157-165.
6. Galbilondo I, Saiz A, Galan L et al. Analysis of relapses in anti-NMDAR encephalitis. *Neurology* Aug 2011
DOI:10.1212/WNL.0b013e31822cfc6b.