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Case Report / Olgu Sunumu

Anti-N-Methyl-D-Aspartate-Receptor Encephalitis in Young Females

Genç Kadınlarda Anti N-Metil-D-Aspartat-Reseptör Ensefalit

Kamlesh Kumari[1], Neeru Sahni[1], Vimla Kumari[2], Vikas Saini[1]

[1]*Department of Anaesthesia and Intensive Care, Postgraduate Institute of Medical Education and Research, Chandigarh, India*

[2]*Department of Gynaecology and Obstetric, Dr. S.N. Medical College Jodhpur, Rajasthan, India*

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Abstract / Öz

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is an immune-mediated disease commonly associated with ovarian teratoma. Anti-NMDA–receptor autoantibodies disrupt NMDA function leading to the development of psychosis, seizures and autonomic dysfunction. The treatment includes underlying tumour resection and immunosuppression. Slow recovery and unpredictable clinical course makes intensive care management of these patients challenging. We report the management of two young female patients with anti-NMDA–receptor encephalitis associated with ovarian teratoma.

Keywords: NMDA, encephalitis, ovarian teratoma

Anti-N-metil-D-aspartat (NMDA) reseptör ensefalit yaygın olarak over teratomu ile ilişkili immün aracılı bir hastalıktır. Anti-NMDA-reseptör otoantikorları psikoz, felç ve otonomik disfonksiyon gelişimine yol açarak, NMDA fonksiyonunu bozarlar. Tedavisi altta yatan tümör rezeksiyonu ve immünosüpresyonu içermektedir. Yavaş iyileşme ve öngörülemeyen klinik seyir bu hastaların yoğun bakım yönetimini zorlaştırmaktadır. Bu çalışmada over teratom ile ilişkili anti-NMDA-reseptör ensefaliti olan iki genç kadın hastanın yönetimi sunulmaktadır.

Anahtar Sözcükler: NMDA, ensefalit, over teratom

Introduction

Anti-N-methyl-D-aspartate (NMDA)–receptor encephalitis is an immune-mediated neurological disorder caused by production of antibodies to the NMDA receptor leading to a syndrome of psychosis, movement disorder, neurologic deterioration and autonomic dysfunction (1, 2). It is predominantly seen in children and young adults (80% females) and is commonly associated with mature ovarian teratoma. Early tumour removal and aggressive immunotherapy are the mainstay of treatment (2). Patients require prolonged intensive care management owing to slow recovery. We report the intensive care management of two young females presenting to our intensive care unit (ICU) with anti-NMDA receptor encephalitis.

Case Presentations

Case 1

A 26-year-old female with initial complaints of headache, decreased sleep and irrelevant talk experienced generalised tonic clonic seizure for which she was admitted to our centre. On admission, her vitals were stable but the Glasgow Coma Scale (GCS) score was $E_4V_2M_4$. Repeated seizures, continuous orofacial dyskinesia and involuntary movements requiring high doses of anticonvulsants and benzodiazepine infusion led to mechanical ventilation and intensive care admission. A cerebrospinal fluid (CSF) analysis showed mildly elevated lymphocytes, and acyclovir was started for presumed viral encephalitis. Electroencephalogram (EEG) showed generalised slowing, and magnetic resonance imaging (MRI) study was normal. In view of her age and the clinical presentation, neurologists considered anti-NMDAreceptor encephalitis a probable diagnosis, which was confirmed by an indirect fluorescent antibody test that showed anti-NMDAreceptor antibodies in the serum and CSF. The patient received intravenous methylprednisolone 1 g day^{-1} for 3 days. In view of anticipated prolonged ventilation, she was tracheotomised on day 7. Contrast-enhanced computed tomography (CECT) of the abdomen revealed presence of right-side ovarian tumour, and right-side oopherectomy was performed on day 11. Anaesthesia was given with intravenous fentanyl, propofol and vecuronium and maintained with desflurane in a mixture of oxygen and air. The surgery was un-

Address for Correspondence/Yazışma Adresi: Kamlesh Kumari E-mail: kamlesh.gmch@gmail.com

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eventful and patient remained haemodynamically stable. The pathological diagnosis of the tumour was mature teratoma of ovary.

With no signs of recovery, she received intravenous immunoglobulin (2 g kg^{-1} divided over 5 days). In 3 months, the frequency of seizures decreased but orofacial dyskinesias and involuntary movements of extremities persisted. Repeat indirect fluorescent antibody test still detected anti-NMDAreceptor antibodies in the CSF. Six cycles of rituximab (375 mg m^{2-1}) were given weekly. Because of insufficient clinical response, 700 mg m^{2-1} cyclophosphamide was added on a once-monthly basis. After the first bolus, a slow but consistent recovery was observed. She gave social smile to her family but there was no response to verbal commands.

In view of continuous immunosuppression and prolonged stay (seven months) in the ICU, she had multiple episodes of ventilator-associated pneumonia (VAP) and central line-associated blood stream infection, which were suspected by increased purulent secretions, increasing oxygen requirement and difficulty in weaning and were confirmed by chest X-ray findings and tracheal and blood culture. Although the tracheal culture grew *Acinetobacter baumanii* on multiple occasions, antimicrobial therapy was gradually de-escalated due to the absence of definitive clinical signs suggestive of sepsis, such as fever and blood reports, showing normal white blood cell count, C-reactive protein (CRP) and procalcitonin levels. She was gradually weaned off the ventilator, shifted out of the ICU in stable condition and later discharged. Currently, she is on regular follow up and is receiving monthly cyclophosphamide.

Case 2

A 24-year-old female patient with similar complaints of headache, irrelevant talk and behaviour, generalised tonic clonic seizure and GCS of $E_2V_2M_5$ required ICU admission. Her EEG was suggestive of localisation-related epilepsy. With normal findings of MRI brain and CSF analysis, the diagnosis of anti-NMDA–receptor encephalitis was confirmed by indirect fluorescent antibody test and intravenous methylprednisolone (1 g day^{-1}) was given for 3 days. For control of seizures, multiple anti-convulsants were started which helped to control seizures but involuntary movements of extremities persisted. CECT of the abdomen revealed bilateral ovarian tumour; however, due to lack of family consent for bilateral oopherectomy and cost constraints to afford further treatment, she was managed medically with anticonvulsants and immunosuppresants. In view of prolonged ICU stay and need of mechanical ventilation, tracheostomy was done on the tenth day of ICU admission. During her one-month ICU stay, there were periods of improvement and decline because of VAP, which was treated with antimicrobial therapy as per culture reports. She was gradually weaned off the ventilator, her seizures were controlled but she remained confused and disoriented and was shifted to ward. The patient was discharged after a month, and she later died at home due to tracheostomy-related complication.

Discussion

High suspicion for anti-NMDA–receptor encephalitis should be considered in young females presenting with acute psychosis, behavioural or personality disturbances, headache, dyskinesia and seizures as early treatment with surgery and immunosuppressive drugs is beneficial (1, 2). The antigenic material NR1 and NR2 subunits of NMDA are expressed by the neural tissue, a component of ovarian teratoma. Swings of haemodynamics due to autonomic instability can be very variable and unpredictable. Central hypoventilation and the need of high doses of anticonvulsants and benzodiazepine infusion to control seizures necessitate mechanical ventilation (3, 4). MRI of the brain is usually normal but EEG is abnormal, mostly showing non-specific, slow and disorganised activity and sometimes epileptic activity. Initial CSF analysis reveals lymphocytosis and sparse oligoclonal bands, which become prominent as the disease progresses (5, 6). For confirmation, there is an indirect fluorescent antibody test that detects antibodies against the NMDA receptor found in patient's serum or CSF (7).

First-line immunosuppressive therapy includes methylprednisolone 1 g day^{-1} for 5 days and concomitant intravenous immunoglobulins (0.4 g kg^{-1} day^{-1} for 5 days) or plasma exchange. Second-line therapy consists of rituximab (375 mg m^{2-1} $week^{-1}$ for 4 weeks) combined with cyclophosphamide (750 mg m^{2-1}) given with the first dose of rituximab, followed by monthly cycles of cyclophosphamide (5). Our first patient showed signs of recovery only after administration of second-line drugs.

Intensive care unit management is challenging as these patients are prone to develop hospital-acquired infections and do not manifest diagnostic clinical signs. The biomarkers of sepsis, such as CRP and procalcitonin, are also misleading and the dilemma in initiation and de-escalation of antimicrobial therapy persists. The difference between an isolated organism being a pathogen or coloniser is a grey zone in such patients. Moreover, due to slow recovery and prolonged illness, these patients need extensive physiotherapy and excellent nursing care.

Anaesthetic management is also challenging as antibodies to NMDA receptor decrease surface density and synaptic localisation via selective antibody-mediated capping and internalisation of surface NMDA receptors (8). When drugs, such as ketamine and nitrous oxide, should be avoided, propofol, volatile agents (isoflurane, sevoflurane and desflurane), vecuronium, rocuronium, remifentanil and fentanyl have been reported to be safe (4, 9, 10).

Conclusion

Anti-NMDA–receptor encephalitis is the disease of young, which needs early recognition, early surgery of the underlying tumour and early immunosuppression. To date, there are no definite guidelines on treatment strategies that may acceler-

ate recovery in these patients. As the recovery occurs at slow pace, ICU management becomes difficult in an immunosuppressed patient prone to nosocomial infections.

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