Olgu Sunumu

A Fatal Case of Anti-NMDA Receptor Encephalitis

Fatal Seyirli Bir Anti-NMDA Reseptör Ensefaliti

Eren GÖZKE [1], Nur AKGÜN [2], Zehra AKTAN [1], Dilek Erdoğan ARI [2]
S. Sinem TAŞDEMİR [1], Ceren KARİP [2], Özlem ALICI [3], Canan AĞALAR [3]

1. Department of Neurology, FSM Teaching and Research Hospital, Istanbul, Turkey
2. Department of Anesthesiology and Reanimation, FSM Teaching and Research Hospital, Istanbul, Turkey
3. Department of Infectious Disease, FSM Teaching and Research Hospital, Istanbul, Turkey

ABSTRACT

Objective: *Anti-NMDA (N-methyl-D-aspartate) receptor antibodies related encephalitis is a rare form of autoimmune encephalitis. We report a case of anti-NMDA receptor encephalitis with fulminant course.*

Case: *A 22-year-old female patient who had abdominal pain and vomiting was seen in the emergency department because of her apathy. On neurological examination she was awake and oriented, but mildly apathic. Cooperation was poor. Fundus examination was unremarkable. There were not any findings for lateralization. She had difficulty in tandem walking. Plantar responses were flexor.*

Cranial MR showed mild intensity changes on the left parahippocampal gyrus without contrast enhancement. CSF analysis revealed the presence of 80/mm3 polymorph lymphocytes. Antiviral and antibiotic therapies were started. Cranial MR was repeated after development of somnolence on 4. day. Extension of the lesion into the left temporal, and occipital lobes with a gyriform, and mild leptomeningeal contrast enhancement was observed. On 12. day, enlargement of the lesion on the right hemisphere was observed on cranial MR. There was no cell in CSF analysis on 13.day. Herpes PCR result was negative.

Antibody panel requested for autoimmune encephalitis revealed NMDA receptor antibody positivity and she was diagnosed as anti-NMDA receptor encephalitis. High dose methylprednisolone added to the treatment. PET-CT performed for investigation of ovarian teratoma did not demonstrate any evidence for malignancy. IVIG, plasmapheresis, and immune adsorption were applied without any clinical benefit. She died on 68. day of her hospitalization, and postmortem oophorectomy was performed. Histopathological examination did not reveal any evidence of teratoma.

Conclusion: *Although prognosis generally better, anti-NMDA receptor encephalitis can be fatal course.*

Keywords: *autoimmune encephalitis, anti-NMDA receptor, overian teratoma*

ÖZET

Amaç: *N-metil-D-aspartat (NMDA) reseptör antikorları ile ilişkili ensefalit seyrek görülen otoimmün ensefalitlerden biridir, Burada fatal seyirli bir anti-NMDA reseptör ensefaliti olgusu sunulmaktadır.*

Olgu: *Karın ağrısı ve bulantı yakınmaları ile acil servise başvuran 22 yaşındaki tkadın hasta dalgınlık ve apati hali nedeniyle istenen konsultasyon sonrası görüldü. Nörolojik muayenede bilinç açık, orientasyon tamdı, ancak apati hali vardı. İyi koopere olmuyordu. Fundus normaldi.*

Taraf bulgusu yoktu ve TDR'ler fleksördü. Adımlamada zorlanıyordu. Kranial MR'da sol parahipokampal girusta hafif intensite değişikliği saptandı. Kontrast tutulumu izlenmedi. BOS incelemesinde 80/mm3 PNL vardı. Ensefalit ön tanısı ile yatırıldı ve antiviral ve antibiyotik tedavisi başlandı. 4. günde somnolans gelişmesi ve kooperasyonun bozulması sonrası kontrastlı MR tekrarlandı. Lezyonun sol temporal ve oksipital loblara yayıldığı, giral tarzda ve hafif leptomeningeal kontrast tuttuğu izlendi. 10.günde epileptik bir nöbet geçirmesi sonrasında valproat başlandı.

12.günde çekilen MR'da lezyonun genişlediği ve sağ hemisferde de dağınık odakların eklendiği görüldü. 13.günde yapılan BOS incelemesinde hücre görülmedi. Herpes PCR sonucu negatifti. Otoimmün ensefalitler yönünden istenen antikor panelinde NMDA reseptör antikoru pozitif bulunarak hastaya anti-NMDA reseptör ensefaliti tanısı kondu. Tedaviye yüksek doz metilprednizolon eklendi. Over teratomu yönünden yapılan PET-CT de malignite lehine bulgu saptanmadı.

İVİG, plazmaferez ve immün adsorbsiyon da yapılan hastada klinik yarar izlenmedi. Yatışının 68. gününde eksitus olan hastada postmortem overektomi yapıldı. Patolojik incelemede teratom saptanmadı.

Anahtar Kelimeler: *otoimmün ensefalit, anti-NMDA reseptörü, over teratomu*

Contact Informatrion
Corresponding **Author:** Eren Gözke
Address: Fatih Sultan Mehmet Teaching and Research Hospital, Department of Neurology, Istanbul, Turkey
Phone: +90 (532) 616 54 52
E-mail: egozke@gmail.com
Submitted: 10.04.2015
Accepted: 22.10.2015

INTRODUCTION

Anti N-methyl-D-aspartate (anti-NMDA) receptor antibody encephalitis has an important place among other types of autoimmune encephalitis. Since its first description in 2007, it has played an important role in the enlightment of similar clinical entities which could not be diagnosed by that time (1). It is often associated with ovarian teratoma in young women, but children and older patients are less likely to have tumors.

Prognosis is poorer in older patients. NMDA receptors are found in all parts of the central nervous system, and play important roles in the mediation of synaptic transmission, plasticity, and excitotoxicity. It has NR1 (glycine), and NR2 (glutamate) subunits. The antibodies against to NMDA receptors reduce the gamma-aminobutyric acidergic inhibition of glutamatergic cells resulting in excessive glutamatergic excitation of prefrontal and subcortical structures (2).

CASE

A 22-year-old female patient applied to the emergency service with complaints of abdominal pain, nausea, vomiting, and headache. She was examined after request for consultation because of apathy. On abdominal ultrasonography requested by an emergency medicine specialist, an ovarian cyst was detected, and a gynecologist recommended symptomatic treatment, and follow-up of the patient. On initial neurological examination she was alert, oriented, but mildly inattentive. Her cooperation and obeying dual commands was poor. Neck stiffness and meningeal irritation were not present.

Fundus examination was unremarkable bilaterally. Horizontal nystagmus was detected on her left gaze. Her muscular strength was intact in four extremities. Deep tendon reflexes were normoactive, and plantar reflexes were flexor. Dysmetria and dysdiadochokinesia were not detected. Her walking was mildly ataxic. Past medical history was unremarkable. But her mother died two years ago because of encephalitis of unexplained cause. On cranial MR, a mild change in the intensity in the left parahippocampal gyrus, and a slightly effaced sulcus were detected.

On diffusion weighted imaging any restriction was not observed. On post-contrast imaging any enhancement was not noted (Figure 1).

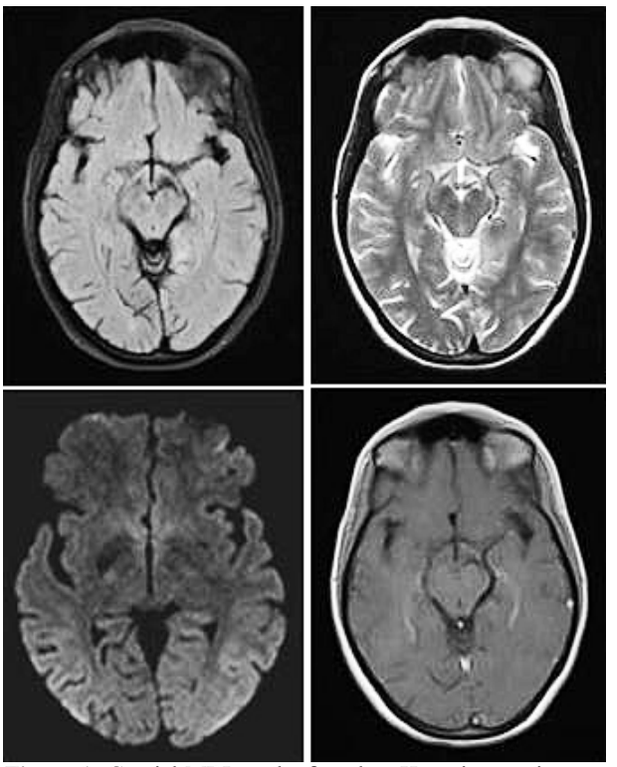

Figure 1: Cranial MRI on the first day: Hyperintense images on the left parahipocampal gyrus, and effacement of the left occipitotemporal sulcus (top left: FLAIR; right: T2 –weighted images). Absence of restricted diffusion (bottom left), lack of contrast enhancement on post-contrast images (bottom right).

Cerebrospinal fluid (CSF) analysis revealed 80/mm^3 polymorphonuclear leukocyte. Other values were within normal limits. A CSF culture, and polymerase chain reaction (PCR) for the probable identification of herpes were requested. The patient was hospitalized with initial diagnosis of encephalitis, and treatment with ceftazidime, metronidazole, acyclovir, and meropenem was initiated. On the second day of her hospitalization, she developed somnolence, her cooperation deteriorated, and a mild degree of neck stiffness started.

Then cranial MRI with contrast was repeated. Increase in the size of the lesion, increased contrast enhancement in gyri, and partial leptomeningeal involvement were observed (Figure 2).

On EEG, neuronal hyperexcitability, and disorganization of the left hemisphere were noted. Valproate was added to the therapy. She had suffered from involuntary twitchings around her mouth, and her consciousness was severely impaired.

The patient did not respond to antibiotic and antiviral treatment. On the 12. day of her hospitalization she experienced tonic-clonic seizures, and repeat cranial MR was obtained which revealed emergence of new lesions on the contralateral hemisphere (Figure 3).

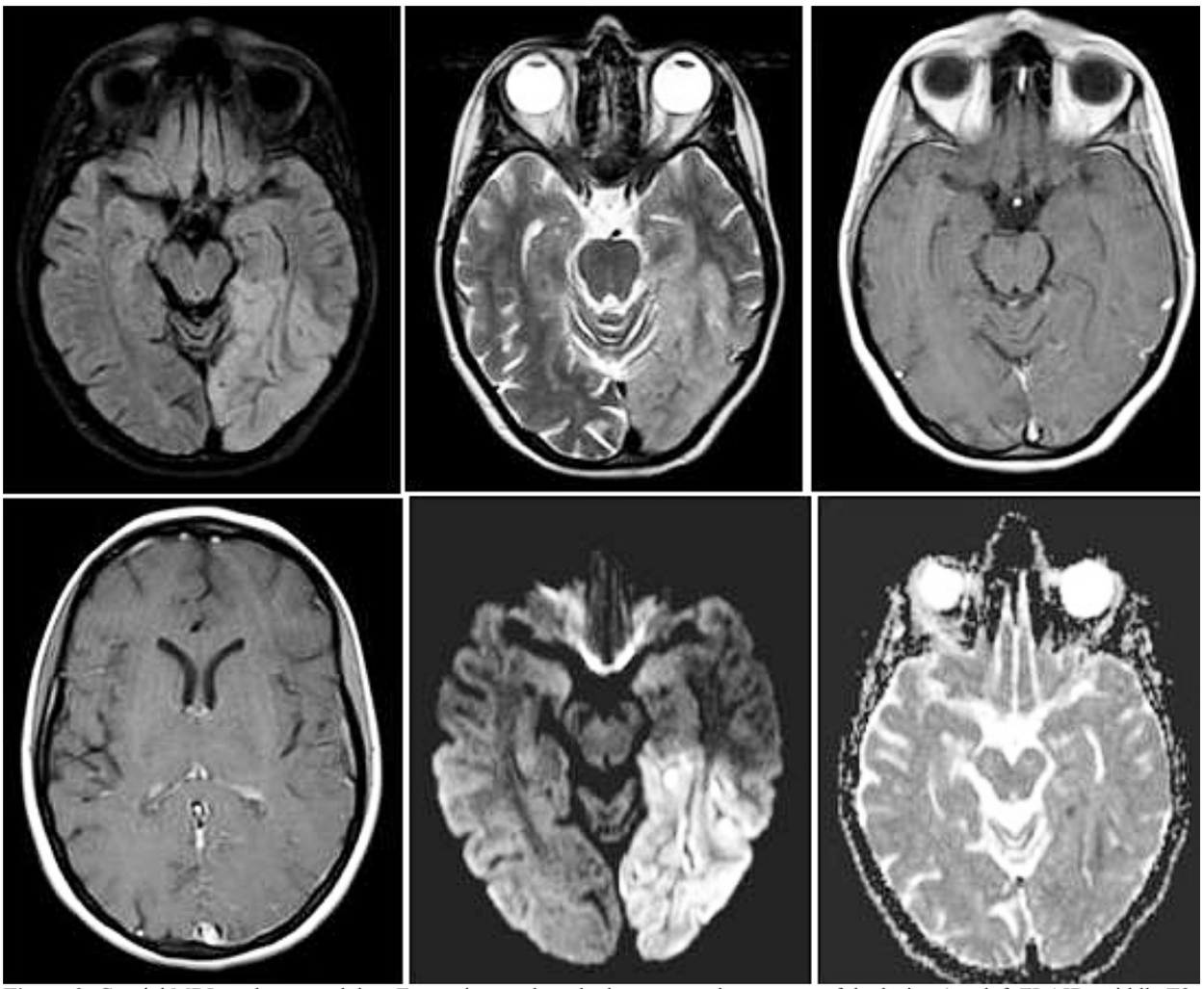

Figure 2: Cranial MRI on the second day: Expansion, and marked contrast enhancement of the lesion (top left FLAIR, middle T2-weighted images). Increased contrast enhancement showing a gyral pattern, partially enhancement in the leptomeningeal area (top right and bottom left). There is marked diffusion restriction (bottom middle), low signal on apparent diffusion coefficient (ADC) are not clear (bottom right).

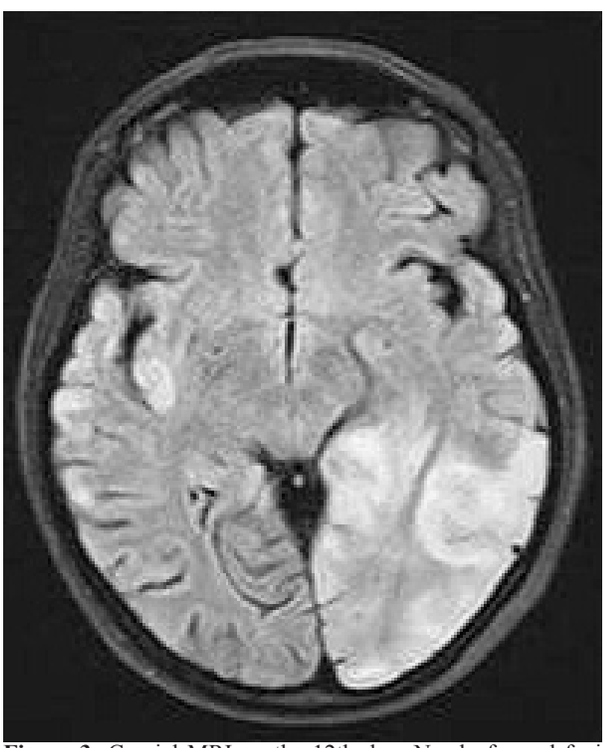

Figure 3: Cranial MRI on the 12th day: Newly formed foci mainly in cortical gray matter involving cortical surfaces of the left frontal, and parietal lobe, right insular cortex, right frontoparietal region, and occipital lobe (FLAIR image).

Her previous herpes PCR, and culture results were not pathologic, and her CSF analysis repeated on the 12. day of her hospitalization did not disclose presence of any cells in CSF. Oligoclonal band was not present. Analysis of serum culture samples did not reveal the presence of West Nile virus, and tick-borne encephalitis.

Since any infectious disease was not detected, autoimmune analyses were requested for the detection of anti-glutamate Type AMPA 1 (Glu1), anti-glutamate Type AMPA 2 (Glu2), anti-CASPR2, anti-LGI 1, anti-GABA B receptor Ab (GABABARB1/B2), and NMDA receptor antibodies. NMDA receptor antibody was found positive.

High doses of methyl prednisolone (1000mg/day), and intravenous immunoglobulin (IVIG) therapy (0,4gr/kg/day) were administered. PET-CT did not demonstrate any evidence of ovarian teratoma. Any other malignancy was not also detected. Glasgow coma scale was worsened and evaluated as 7 point.

She developed severe dysautonomia which necessitated her transfer to the intensive care unit. The patient was quadriplegic and need mechanical ventilation. Because of no response to IVIG therapy, plasmapheresis was initiated on the 23. day of her hospitalization. Plasmapheresis sessions were performed daily for the first three days, and then three additional sessions were applied every other day. A good response was not elicited, and immune adsorption therapy was started on the 41. day of her hospitalization. At the end of the sixth session, therapy was terminated because of emergence of epistaxis, and subcutaneous bleeding.

On neurological examination performed on the 48. day, she had an open conscious without any cooperation. Pupils were isochoric with normal light reflexes. Extremities were flask without any response to painful stimuli. Deep tendon reflexes could not be elicited. Plantar reflexes were irrelevant bilaterally. A new cranial MRI obtained at the same day demonstrated a diffuse involvement (Figure 4).

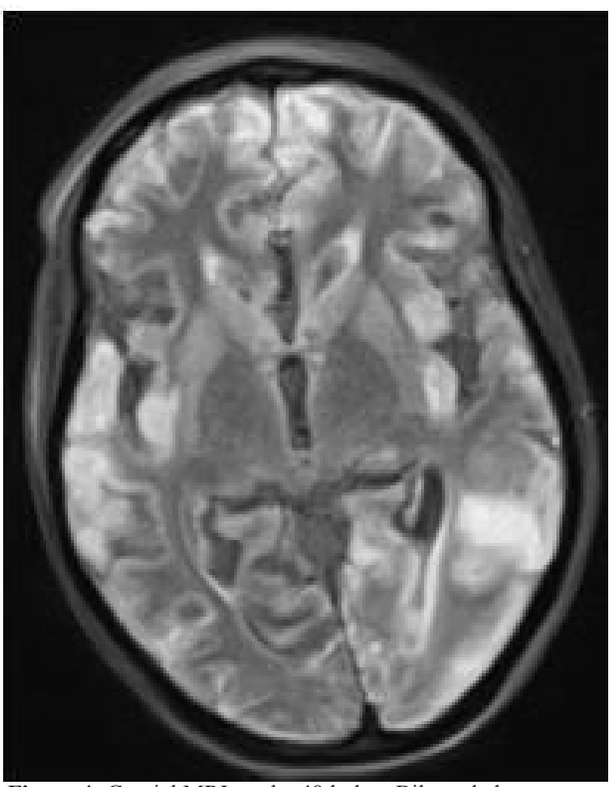

Figure 4: Cranial MRI on the 48th day: Bilateral changes secondary to encephalitis in all lobes all along the corticosubcortical gyri on subcortical areas slightly cystic, and encephalomalasic changes (FLAIR image).

During monitorization, dysautonomia of the patient became more serious, and she died on the 68. day of her hospitalization.

After written approval of the family was obtained, histopathological examination of the bilateral postmortem oophorectomy specimens could not reveal any evidence of teratoma.

DISCUSSION

Anti-NMDAR encephalitis is a clinical entity characterized by multiple symptoms including impaired consciousness, memory deficits, psychotic manifestations, movement disorders, and dysautonomia. Its association with tumoral masses including predominantly ovarian teratoma is a frequently encountered condition. It constitutes 4 % of all cases of encephalitis. It is the second mostly seen autoimmune encephalitis after acute disseminated encephalomyelitis (ADEM). Antibodies are formed against NR1 subunit of NMDA receptor. In 70 % of the cases, prodromal symptoms including headache, vomiting, nausea, diarrhea, and upper respiratory tract infection are detected (3).

In general; psychiatric symptoms such as anxiety, insomnia, delusions, and mania become manifest within a few days. Since loss of immediate memory is not in the foreground, the patient is generally examined by psychiatrists. Social withdrawal and stereotypical behavior are sometimes seen.

Speech disorders including restricted verbal output and mutism usually become apparent at a later date. Gradually, movement disorders as agitation, catatonia, orofaciolingual dyskinesias, and dystonia, epileptic seizures, and dysautonomia are added to this clinical picture. The most frequent autonomic manifestations include hyperthermia, tachycardia, hypersalivation, hypertension, bradycardia, hypotension, urinary incontinence, and erectile dysfunction.

Mechanical ventilation might be required because of hypoventilation. It may be necessary even if the level of consciousness is relatively preserved. In 50 % of the cases, cranial MR can be normal. In the remaining 50 % of the cases, on T2 weighted images, hyperintensities can be observed in hypocampus, cerebral and cerebellar cortex, frontobasal, and insular area, basal ganglions, brainstem, and rarely spinal cord. Frequently slightly contrast enhancement can be seen. CSF is normal in 80 % of the cases. Pleocytosis, and increased protein levels are observed. Frequently NMDAR antibodies are found in CSF and serum.

Antibodies may persist in CSF, if diagnosis is delayed. Besides, after the treatment antibodies can disappear from serum, and appear in CSF. Cerebral biopsy does not contribute to the diagnostic work-up. Female patients constitute 80 % of the cases.

The disease is frequently encountered in children, and adolescents. Female patients should be investigated especially for the presence of ovarian teratoma.

Associated tumor risk is detected in 5 % of the male patients under the age of 18. Seventy-five percent of the cases improve with severe or mild sequelae. Its mortality rate is at the level of 4 percent. In the treatment, steroids, IVIG, and plasmapheresis are used. If adequate response is not elicited, then rituximab, and cyclophosphamide can be used. If detected, teratoma or any other tumor should be removed (4, 5).

In conclusion, although prognosis generally better, anti-NMDA receptor encephalitis can be fatal course.

REFERENCES

1. Dalmau J, Tüzün E, Wu HY, Masjuan J, Rossi JE, Voloschin A, Baehring JM, Shimazaki H, Koide R, King D, Mason W, Sansing LH, Dichter MA, Rosenfeld MR, Lynch DR. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol. 2007;61(1):25-36.

2. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, Dessain SK, Rosenfeld MR, Balice-Gordon R, Lynch DR. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol. 2008;7(12):1091-8.

3. Nath U, Warren NM, Ali H. NMDA receptor encephalitis--expanding the clinical spectrum. BMJ Case Rep. 2011 Jul 28;2011.

4. Titulaer MJ, McCracken L, Gabilondo I, Iizuka T, Kawachi I, Bataller L, Torrents A, Rosenfeld MR, Balice-Gordon R, Graus F, Dalmau J. Late-onset anti-NMDA receptor encephalitis. Neurology. 2013;81(12):1058-63.

5. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol. 2011;10(1):63-74.