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# Postoperative Anti–N-methyl-D-aspartate (NMDA) Receptor Encephalitis After Surgical Resection of Teratom

**Selin Özaltın**

## *Teratomun Cerrahi Rezeksiyonu Sonrası Gelişen Anti-N-metil-D-aspartat (NMDA) Reseptör Ensefaliti*


### ABSTRACT

*Anti–N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a form of autoimmune and paraneoplastic encephalitis that is commonly encountered in young women with ovarian teratoma. As an encephalopathy with possible epileptic, extrapyramidal and psychiatric manifestations, the treatment requires both tumor resection and immunosuppression. However, the rarity of the disease and lack of knowledge most often cause the accurate diagnosis to be late for the optimal patient outcome. Herein, we report a case of a 33 year-old female with anti-NMDAR encephalitis that interestingly developed after the surgical resection of ovarian teratoma.*


***Keywords:*** *paratesticular, mullerian, adenomatoid*


### ÖZ

*Anti-N-metil-D-aspartat reseptörü (anti-NMDAR) ensefalit, over teratomu olan genç kadınlarda sıklıkla karşılaşılan bir otoimmün ve paraneoplastik ensefalit şeklidir. Muhtemel epileptik, ekstrapiramidal ve psikiyatrik belirtileri olan bir ensefalopati olarak, tedavi hem tümör rezeksiyonu hem de immünosüpresyon gerektirir. Burada, over teratomunun cerrahi rezeksiyonu sonrası ilginç bir şekilde gelişen anti-NMDAR ensefalitli bir 33 yaşındaki kadın hastayı sunuyoruz.*


***Anahtar kelimeler:*** *paratesticular, mullerian, adenomatoid*

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## INTRODUCTION

Tumor cells have been found to cause symptoms not related to tumor invasion or compression [1]. Defined as paraneoplastic syndromes, these symptoms can result from the secretion of peptides, hormones and cytokines from the tumor, or can occur due to an immune cross-reactivity between the tumor and normal tissue [2].

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is accepted as a paraneoplastic neurologic syndrome (PNS) because of its association with ovarian teratoma [3]. The first paper describing this association was published by Dalmau and colleagues in 2007 [4]. A teratoma triggers an immune sensitization by producing onconeural antibodies against NR1a and NR2b subunits of the NMDA receptor, resulting in glutamate-mediated dysfunction [3].These receptors are found in high density in the frontotemporal region, and are involved in many functions such as behavior, memory, learning and synaptic spasticity [5]. Therefore, anti-NMDAR encephalitis is defined by psychotic encephalopathy, epilepsy, facial abnormalities, changes in consciousness and hypoventilation as its significant clinical features [6].

In this paper, we would like to report a case of anti-

NMDAR encephalitis occurring after the surgical removal of a teratoma. The diagnosis was hardly made because of the atypical presentation.

## CASE REPORT

A 33 year-old Caucasian woman was admitted to our clinic with initial complaint of pelvic pain that has been present for 3 months. She reported a previously performed transvaginal ultrasound (TVU) showing a 85x70 mm cyst. Her medical history showed no abnormality while her surgical history included one caesarean section. Her pelvic examination revealed a normal size uterus with a 7x6 cm left ovarian mass. TVU showed a 80x70 mm septated ovarian cyst with mixed heterogeneity. Pelvic magnetic resonance imaging (MRI) confirmed the finding. CA125 and AFP levels were 16 u/ml, 2.5 ng/ml respectively. The patient opted for surgical approach.

The inspection during the surgery revealed a 8 cm left ovarian mass with no additional finding. Therefore, left laparoscopic salpingo-oophorectomy was performed (Figure 1). The cyst was aspirated before removing in an endobag. No further actions were taken after the frozen section, and the pathological diagnosis was benign teratoma. The patient was discharged on postoperative day 1.

On postoperative day 9, the patient presented to the emergency department with increased forgetfulness, anxiety and insomnia, followed later by dystonia. The symptoms were thought to be psychiatric and the patient was referred to the psychiatry department. Neurologic examination and cranial MRI showed no abnormality. The preliminary diagnosis was dissociative disorder following traumatic event, and treatment with escitalopram and quetiapine was started. The following day, the patient's condition deteriorated: she developed hand tremor, generalized dystonia and akathisia. Her confused state prompted the diagnosis of encephalopathy. 1 mg lorazepam was started, and the patient reported feeling better with this treatment. Daily electroencephalogram (EEG) was normal (Figure 2).

On postoperative day 12, the patient experienced generalized tonic-clonic seizure and loss of conscious. Her blood analysis were normal. Tuberculosis DNA polymerase chain reaction (PCR) resulted nega-

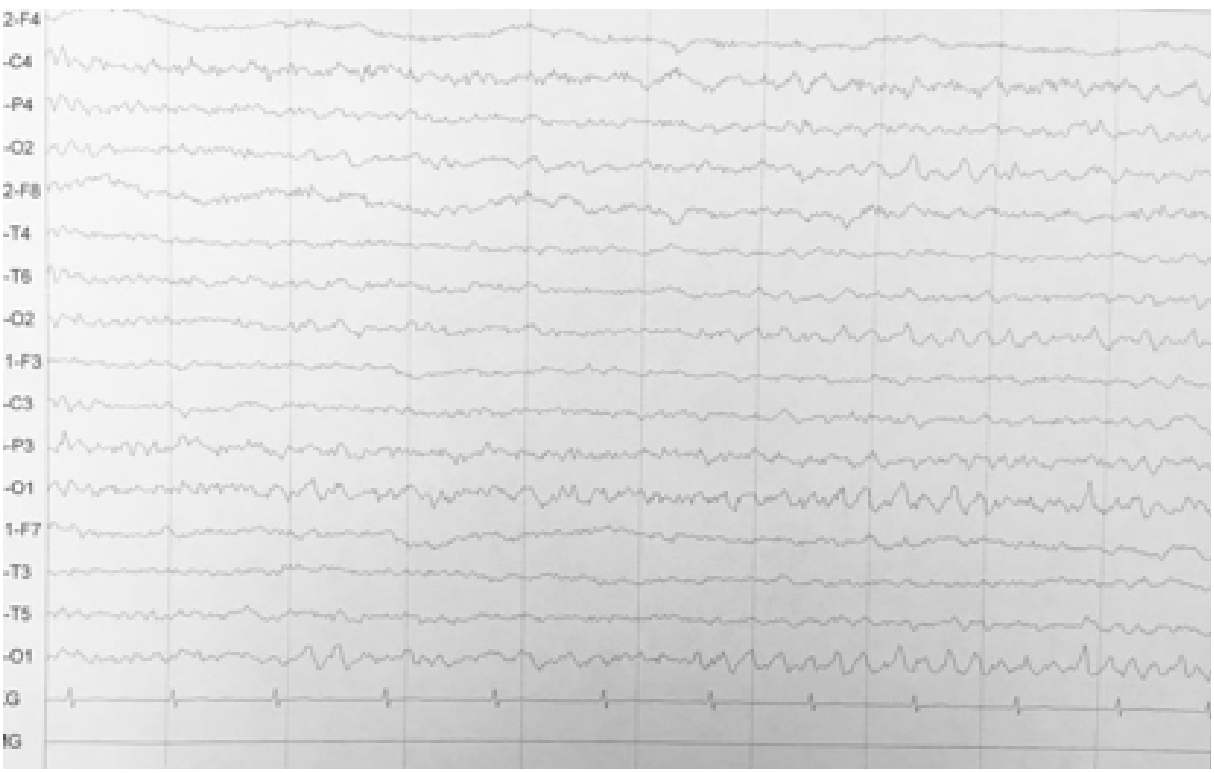


**Figure 1. Rhythmic slow wave activity.**

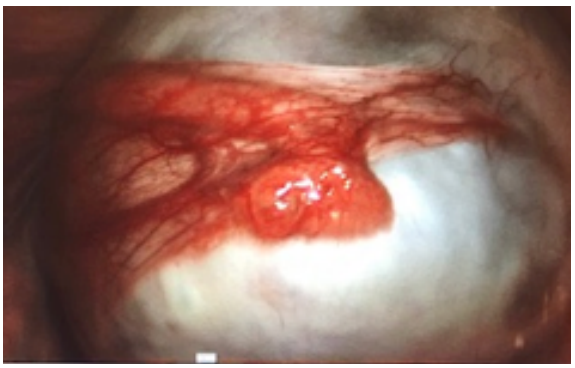

**Figure 2. Left ovary.**

tive. A lumbar puncture (LP) revealed normal level of glucose, slightly increased level of protein and lymphocytic pleocytosis (55 leukocytes /mm$^3$). Culture of cerebrospinal fluid (CSF), Epstein-Barr Virus DNA PCR, Herpes Simplex Virus (HSV) DNA type 1 and 2 PCR, Varicella-Zona Virus DNA PCR were negative. Two more generalized tonic-clonic seizures occurred following the LP. The patient was admitted to the intensive care unit (ICU) where she was started on multidrug treatment consisting of diazepam, phenytoin and levetiracetam. The preliminary diagnosis of HSV and autoimmune encephalitis were considered, and acyclovir and IVIG were started. CSF HSV PCR analysis was repeated. Acyclovir was stopped when the result came negative. On the 6th day of IVIG treatment, patient experienced increased agitation and hallucinations, thus the treatment was switched to pulse steroid. A workup for paraneoplastic syndromes was conducted including breast and abdominal ultrasound, thorax computed tomography (CT), abdominal and cranial MRI. Analysis of serum and CSF for anti-NMDAR antibodies revealed positive. The patient recovered fully with immunosuppressive therapy without any sequela.

The final pathologic result of the specimen was reported as immature teratoma On postoperative day 40, after the patient was considered stable and strong enough to undergo a surgery, laparoscopic staging procedure was performed. Any other additional tumor wasn't found in the final pathology.

## DISCUSSION

With an estimated prevalence of 8% in all cancer patients,7 paraneoplastic syndromes, if displayed before the cancer diagnosis, can impact the prognosis by providing curable treatment for early stages. This favorable outcome is mostly seen with paraneoplastic neurologic syndromes (PNS) [8].

PNSs are seen in 1% of cancer patients overall [9]. The key mechanism is the production of tumor-directed antibodies, known as onconeural antibodies, that are associated with onconeural antigen-specific T lymphocytes [10]. These antibodies and lymphocytes attack the nervous system (central nervous system, neuromuscular junction or peripheral nervous system) causing permanent damage, therefore tumor resection doesn't cure the syndrome: immunosuppressive therapy remains the main treatment. The diagnosis of PNSs is not easily recognized: infectious, toxic and metabolic etiologies should be addressed. Once the diagnosis of a PNS is made, an extensive workup has to be conducted in order to find out the underlying tumor.

Anti-NMDAR encephalitis has 5 stages: [6,11,12] (1) the prodromal stage similar to a cold or viral infection, (2) the psychiatric stage characterized with memory loss, hallucinations, personality changes, (3) the no reaction stage along with dissociative and unresponsive features (akinetic, catatonia-like state), (4) the excessive movement stage, and finally (5) the recovery stage. The disease remains important because of its potential to alert the physician for an synchronous or upcoming teratoma, and especially for immature type [13]. 12-45 years old is the range when the association of anti-NMDAR encephalitis with ovarian teratoma is the highest [14]. The development of ovarian teratoma after the treatment of anti-NMDAR encephalitis has been reported in some papers,15-20 therefore, a regular tumor screening should be established in these patients.

We aim to report an atypical presentation of anti-NMDAR encephalitis. Normally, encephalitis occurs before or simultaneously with the detection of ovarian teratoma. However, in our case, the clinical presentation developed after the surgical removal of the teratoma. Even though it is recommended to remove the teratoma when anti-NMDAR encephalitis is diagnosed, [21] we would like to remember that surgery isn't enough, and immunosuppressive therapy targeting the onconeural antibodies who are responsible of the clinical presentation and remain in the body after the surgery shouldn't be underestimated. Thus, we strongly recommend immunother-

apy that includes corticosteroids, IVIG and plasmapheresis as the main therapy or in combination with surgical approach.

Another point we would like to underline is the difficulty encountered during the diagnosis. Anti-NMDAR encephalitis can be often mistaken for other diseases: similar symptoms are seen in mental diseases or viral encephalitis [6]. If the patient is a young female between 12-45 years old, who has encephalitis of undetermined etiology along with psychiatric symptoms and seizures, a low threshold should be adopted for the diagnosis. Brain MRI is normal in half of the patients. Possible abnormal findings include high signals in cerebellum, cortex and medial temporal lobe [4]. EEG is useful since generalised extreme delta brush is unique in these patients. Additional findings such as diffuse background slowing with delta slow waves, indicating diffuse cortical damage, might be observed as well [22]. CSF analysis, except for anti-NMDAR antibodies, reveals nonspecific inflammatory reactions [23]. The most specific and critical finding is the detection of anti-NMDAR antibodies in serum and CSF [21].

Ovarian teratoma and anti-NMDAR encephalitis are two diseases with a proven association. Atypical presentations can be observed, however, a high clinical suspicion would help in accelerating the diagnosis and thus, starting the appropriate treatment earlier. This patient would be followed on regular basis for development of another teratoma in the other ovary.

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