

Anti-NMDA Receptor Encephalitis: a Neuropsychiatric Entity

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ABSTRACT

Anti-NMDA receptor encephalitis: a neuropsychiatric entity

Anti-NMDA receptor encephalitis is a form of autoimmune encephalitis which manifests itself with acute or subacute onset psychiatric symptoms, seizures, autonomic dysfunction, and movement disorders. It is a rather recently described form which may progress fatal at about 20%, and which may recover with aggressive immunosuppressive treatment without any sequela. Multifocal, non-specific, subcortical white matter lesions can be observed in cranial magnetic resonance imaging. Since mostly it has paraneoplastic etiology, it is crucial to screen for malignancies after the diagnosis. Its diagnosis is very important, because it will lead early diagnosis of a possible malignancy. In the present article, a case which applied to our outpatient clinic with noisy neuropsychiatric clinical picture, and was diagnosed with anti-NMDA receptor encephalitis after evaluations, and treated with complete recovery, was presented.

Keywords: Immunosuppressive therapy, neuropsychiatric symptoms, paraneoplastic autoimmune encephalitis

ÖZET

Anti-NMDA reseptör ensefaliti: Bir nöropsikiyatrik antite

Anti-NMDA reseptör ensefaliti; akut veya subakut başlangıçlı psikiyatrik semptomlar, nöbet, otonomik disfonksiyon ve hareket bozuklukları ile kendini gösteren bir otoimmün ensefalit türüdür. Yüzde 20 oranında fatal seyredabilen, agresif immünsüpresif tedaviyle sekelsiz iyileşmenin görülebildiği, nispeten yeni tanımlanmış, bir formdur. Kraniyal manyetik rezonans görüntülemesinde multifokal, spesifik olmayan, subkortikal beyaz cevher lezyonları görülebilir. Çoğunlukla paraneoplastik etiyolojiye sahip olması nedeniyle tanı sonrasında malignite taraması önem arz eder. Tanı konulması, muhtemel bir malignitenin erken tanısına olanak sağlaması açısından oldukça önemlidir. Yazımızda gürültülü nöropsikiyatrik tablo ile polikliniğimize getirilen, yapılan değerlendirmeler sonucunda anti-NMDA reseptör ensefaliti tanısı alan ve tedavi ile tam düzelmenin görüldüğü bir olgu sunulmaktadır.

Anahtar kelimeler: İmmünsüpresif tedavi, nöropsikiyatrik belirti, paraneoplastik otoimmün ensefalit

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INTRODUCTION

Anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis has been first defined in 2007, and it is a type of autoimmune encephalitis, which manifests itself predominantly with acute or subacute onset of neuropsychiatric symptoms accompanied by seizures, autonomic dysfunction (1,2). Multifocal, non-specific, subcortical white matter lesions may be observed in 30% of cranial magnetic resonance imaging (MRI) examinations (3). As it is commonly has a paraneoplastic etiology, malignancy screening is important after the diagnosis (2).

CASE

A 46 years old male patient who worked as a welder in the heavy metal sector was brought to our neurological outpatient clinic with complaints of excessive sweating and flares accompanied by numbness in his left side of the face, imbalance, gait problem for a couple of weeks accompanied by speaking a lot and insomnia.

In the neurological examination, his consciousness was open; the patient had marked psychomotor agitation, disinhibited behaviors, and concentration problems. His speech content was disorganized, and

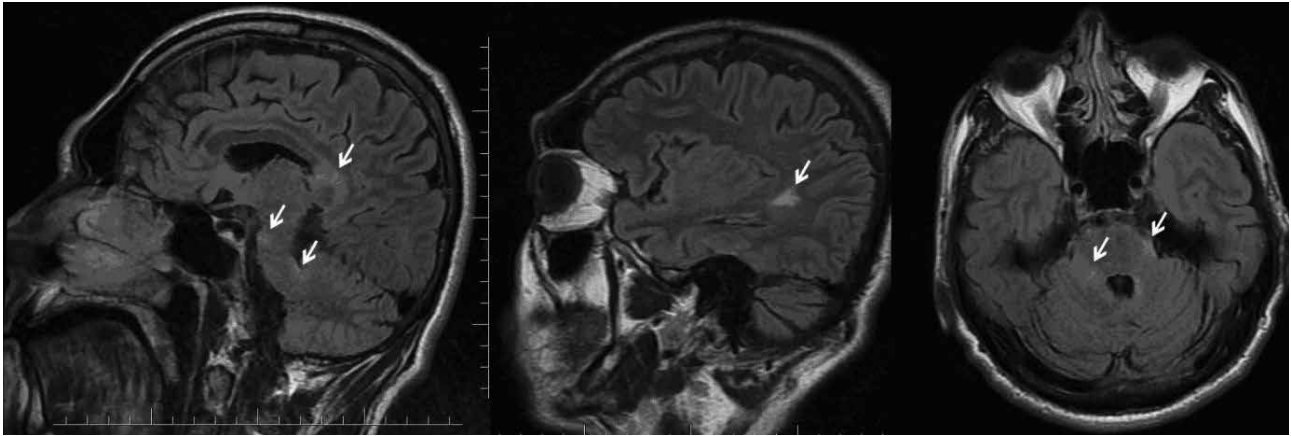


Figure 1: In cranial MRI, isointense lesions were observed bilaterally in cerebral and cerebellar peduncles, pons, corpus callosum, splenium level and subcortical periventricular white matter in T1A sequence, whereas hyperintense lesions in T2A sequence

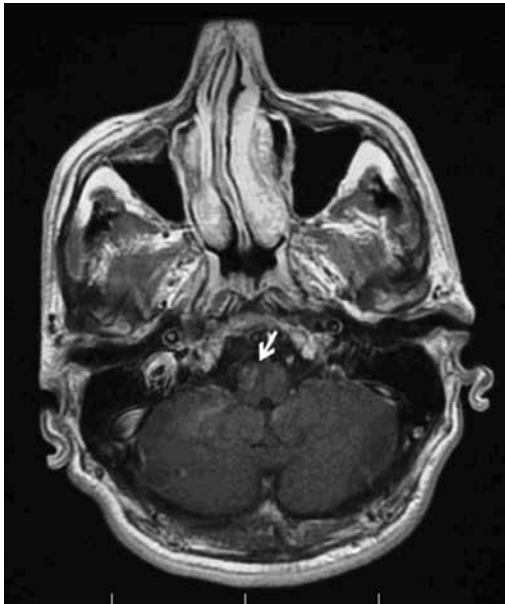


Figure 2: Contrast enhancement observed in infratentorial lesions

he had logorrhea. His articulation was severely cerebellar dysarthric, and he had an ataxic gait.

In cranial MRI examinations, isointense lesions in T1A and hyperintense lesion in T2A sequences were observed bilaterally in cerebral and cerebellar peduncles, pons, corpus callosum, splenium level, and subcortical periventricular white matter (Figure 1A). There was contrast enhancement in infratentorial lesions (Figure 2).

All autoantibodies and metabolic values related to possible vasculitic processes were determined within normal limits in blood samples. No sign in favor of infection was determined in lumbar puncture sampling, with no cultural growth. Viral panel study was observed negative. As anti-NMDA receptor antibody was detected positive in the paraneoplastic panel studies in cerebrospinal fluid, methylprednisolone treatment was started at 1gr/day dose, and the treatment was completed to 7 days. As the patient did not respond markedly to corticosteroid treatment, plasmapheresis treatment was performed every other day for a total of 7 times. Dramatically improvements were observed in cognitive and neurological signs of the patients by plasmapheresis. He needed no longer haloperidol treatment which was given to control his agitation up to 15mg/day when he refused to take orally. Quetiapine which was started as a routine treatment and increased up to 600mg/day dose was also tapered down. After discontinuation of antipsychotic treatment, no agitation and disinhibition was observed in the patient. No positive sign was determined neither in thoracoabdominal tomography and scrotal ultrasonography to screen malignancy, nor in positron emission tomography. Oral methylprednisolone and azathioprine treatments were initiated, and steroid treatment was tapered down. The patient is still being followed up with 100mg/day azathioprine treatment.

DISCUSSION

Anti-NMDA receptor encephalitis is an autoimmune type of encephalitis which is developed by IgG type antibody development to NR1 subunits of NMDA glutamate receptors (4). As awareness of clinicians is increased about the diagnosis, and laboratory facilities are more widely used, number of reported cases in the world is increased rapidly. In a multi-center, prospective study performed in England, it was showed that antibodies against NMDA receptors were responsible for 64% of all encephalitis cases, and that the second most common cause of acute disseminated encephalomyelitis among immune-mediated encephalitis (5,6).

Of patients who are diagnosed with anti-NMDA receptor encephalitis, 80% are females. In a screening performed on 400 individuals, neoplasia was encountered in 59%, and nearly all of them showed teratoma characteristics (7). In some recent studies, it is shown that anti-NMDA receptor antibody production might be triggered during Herpes simplex encephalitis (HSE), and encephalitis might be clinically overt (8). We could not show HSE and malignancy in our patient, but we included him into an intermittent screening program for malignancy.

In 70% of patients, acute-subacute onset psychiatric symptoms which appear in a couple of days-weeks time following prodromal symptoms such as headache, nausea, vomiting are observed. Commonly encountered initial symptoms are paranoia, grandiose delusions, hallucinations, mania, anxiety, and insomnia (7). As in our case, manic symptoms were quite noisy, we transiently transferred the patient to the psychiatry clinic for a better early period of sedation.

It is reported that due to characteristics of initial symptoms, 70-77% of patients are firstly evaluated by a psychiatrist (7,9). However, as it is a newly defined and rarely encountered entity, awareness of anti-NMDA receptor encephalitis is limited among clinicians. In a survey study performed on 76 psychiatrists in Japan, 48.7% reported that they knew

nothing about this disease, whereas 30.3% heard only the name of the disease (10). Although it is reported that delay in diagnosis might result in death in aggressively progressive cases, there were cases diagnosed after treated as schizophrenia for 7 years (11). While neurological signs may accompany the clinical picture from the beginning of acute period, they may be added up later on due to progressive course or they may appear years later during a recurrence (12). In our case, positive neurological examination signs were observed in the background because of the severe psychiatric picture. In cranial MRI, 50% of patients may show hyperintensity in T2A and FLAIR sequences with mild meningeal contrasting in hippocampus, cerebral-cerebellar cortex, frontobasal and insular areas, and in brain stem elements. In 80% of patients, antibody can be shown in CSF sampling or antibody may become positive in repetitive CSF and serum samples (9). In our case, there were parenchymal lesions with contrast enhancement and positive NMDA receptor antibody in CSF.

Administration of high dose steroid, intravenous immunoglobulin or plasma exchange as a first line treatment followed by planning a treatment for a possible malignancy is recommended. If there is a delayed diagnosis or no tumor is detected, then cyclophosphamide or rituximab may be added on the treatment (7). With appropriate treatment complete remission or remission with a mild sequela is observed in 75% of patients (9). In our case, oral steroid and immunosuppressive treatments were given after plasmapheresis, and he recovered without any sequela.

Contribution Categories	Name of Author
Follow up of the case	A.T., S.B., E.E., Y.S.K.
Literature review	A.T., S.B., E.E., Y.S.K.
Manuscript writing	A.T., S.B.
Manuscript review and revision	A.T., S.B., E.E., Y.S.K.

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