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## Anti-NMDA Receptor Encephalitis in a Patient with Rheumatoid Arthritis

To the Editor:

Anti-NMDA receptor (NMDAR) encephalitis is a form of autoimmune encephalitis that was first described in young women with ovarian teratoma<sup>1</sup>. We report the case of a 61-year-old woman with seropositive rheumatoid arthritis (RA) who developed a non-paraneoplastic encephalitis related to antibodies against NMDAR in serum and cerebrospinal fluid (CSF).

Her medical history included dyslipidemia and RA. For the latter, she had received various immunosuppressive agents (sulfasalazine, leflunomide, and etanercept) and was at presentation under treatment with methotrexate (MTX) and rituximab (RTX). She presented with dizziness, unsteady gait, and proximal muscle weakness. No seizures, dyskinesias, autonomic dysfunction, or behavioral changes were present. Outpatient examination was performed, including head and cervical magnetic resonance imaging, whole-body computed tomography (CT), cerebral single photon emission-CT scan, and neurophysiological studies; nothing relevant was found. Nevertheless, RTX was preventively suspended and treatment with MTX in monotherapy was continued. Other concurrent medications were suspended to evaluate their possible implication in the clinical picture, but no relationship was found. Three months later, as cognitive impairment, memory loss, and speech problems were observed, she was hospitalized. Laboratory findings showed a raised erythrocyte sedimentation rate (31 mm/first h, normal < 20) and C-reactive protein (9 mg/l, normal < 5). Full blood count, biochemical serum tests, and coagulation studies were normal. Rheumatoid factor (which had previously been positive), and antibodies for antinuclear, anti-smooth muscle, anti-mitochondrial, anti-neutrophil cytoplasmic, and anti-liver-kidney microsome were negative. Serological testing for hepatitis B and C virus and human immunodeficiency virus were negative. Anti-NMDAR immunoglobulin G (IgG) antibodies against NR1 subunit were found to be positive in blood. CSF analysis showed high protein levels (120 mg/dl, normal < 45), 16 white cells/ml, oligoclonal bands, and anti-NMDAR antibodies. CSF PCR for herpes simplex virus, varicella zoster virus, enterovirus, Toscana virus, and borrelia were negative. Tests for prion disease and the JC polyomavirus were negative. In view of these data, the diagnosis of anti-NMDAR encephalitis was made. Screening for underlying malignancy, including gynecologic ultrasound and total body positron emission tomography-CT, was negative. The patient was treated with intravenous immunoglobulin (0.4 g/kg/day for 5 days) with notable clinical improvement maintained after a 12-month followup.

Anti-NMDAR encephalitis was first described in 2007 as a form of autoimmune encephalitis that most frequently affected young women with ovarian teratoma<sup>1</sup>. So far, well over 500 cases have been described, showing that this disorder is also seen in men and in patients of all ages (8 mos to 84 yrs), and that it is associated with an underlying teratoma in about 60% of adult cases<sup>2,3,4,5</sup>. Anti-NMDAR encephalitis is a multistage disease. The characteristic clinical picture begins with prodromal symptoms such as headache, fever, vomiting, and nausea. Within a few days, patients develop psychiatric symptoms including anxiety, insomnia, mania, and paranoia. The following stage is characterized by decreased responsiveness, autonomic instability, and movement disorders (dyskinesias). The oral-lingual-facial dyskinesias are the most characteristic, but other abnormal movements such as opisthotonic postures and a catatonic state may also occur<sup>3</sup>. Invasive ventilation and admission to an intensive care unit are frequently necessary.

Diagnosis is based on the detection of IgG antibodies against the NR1 subunit of the NMDAR in serum and/or CSF. These antibodies cause capping, crosslinking, and internalization of the NMDAR with the subsequent loss of NMDAR-mediated synaptic function<sup>6</sup>. Treatment should be promptly established with tumor resection in case of an underlying malignancy and/or immunotherapy. First-line treatment consists of corticosteroids, intravenous immunoglobulin, and/or plasma exchange. RTX, cyclophosphamide, or both could be considered in refractory cases. In the series of cases described by Titulaer, *et al*, immunotherapy and tumor removal, if applicable, resulted in important neurological improvement in 80% of patients after a 24-month followup<sup>5</sup>. However, relapses occur in 12–24% of patients with anti-NMDAR encephalitis<sup>5,7</sup>.

Anti-NMDAR encephalitis is a disorder associated with antibodies against the NR1 subunit that results in a characteristic neuropsychiatric syndrome. To our knowledge, we report the first case of anti-NMDAR encephalitis in a patient with longterm seropositive RA. This case is exceptional because of its atypical presentation — dizziness, unsteady gait, and proximal muscle weakness developing over a protracted period — and the observation that the syndrome developed while under biologic therapy.

This case is a reminder that unusual presentations of rare autoimmune diseases may occur in partially treated individuals. A comprehensive clinical and diagnostic evaluation should be performed in all patients presenting with new symptoms and signs that are atypical of rheumatological disease.

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