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LETTER TO THE EDITOR

# Persistence of anti-NMDAR antibodies in CSF after recovery from autoimmune encephalitis

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Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is characterized by psychiatric and neuropsychiatric manifestations preceded by prodromal symptoms in about 70% of patients. It can occur as an autoimmune antibody-mediated non-paraneoplastic syndrome or as a paraneoplastic disorder, triggered by different tumors, more often an ovarian teratoma. NMDARs are localized in neuronal post-synaptic membranes and play a role in synaptic transmission and plasticity. In vitro and in vivo investigations confirm that anti-NMDAR antibodies cause a selective and reversible decrease in NMDAR surface protein directly associated with the level of the antibody titers [1]. Anti-NMDAR antibodies can be detected in the cerebrospinal fluid (CSF) and serum of affected patients, but often they are found only in the CSF. Previous data have confirmed that anti-NMDAR antibodies are more frequently present in both serum and CSF in patients with ovarian teratoma than in subjects without a tumor, suggesting that they can act as a trigger of autoimmune process [2]. In anti-NMDAR encephalitis, the correlation between antibody titers, relapses, and outcome is currently unclear.

In January 2015, a previously healthy 25-year-old woman was referred to a Neurology Unit for flu-like symptoms, confusion, and hallucinations. The patient became rapidly unresponsive and was transferred to intensive care unit. Brain magnetic resonance imaging was unremarkable and electroencephalogram showed diffuse slowing without epileptiform activity. Blood tests noted only a severe hyponatremia and the presence of low titer anti-thyroid peroxidase and thyroglobulin antibodies. CSF analysis showed lymphocytic pleocytosis (360 cells/μL with 98% lymphocytes); extensive viral PCR and cultures ruled out an infectious etiology. She was treated with acyclovir and intravenous corticosteroids with a progressive tapering. At the end of February, CSF analysis revealed the presence of anti-NMDAR antibodies that were absent in serum. The patient was moved to the rehabilitation unit with a progressive and complete neurological recovery. In April 2015, neuropsychological evaluation revealed normal working memory, as well as attention and logical-deductive abilities; the Mini-Mental State Examination score was 30/30. In June and October 2015, anti-NMDAR antibodies were still present only in the CSF, despite a normal neurological and neuropsychological examination. On referral to our hospital, in November 2015, a pelvic ultrasound disclosed a cystic left ovarian mass. In March 2016, anti-NMDAR antibodies were still present in the CSF. After the removal of the cystic mass, microscopic examination confirmed the diagnosis of a mature teratoma. We therefore tested the patient's serum and CSF both in the acute phase and during the follow-up with fixed-cell based essay (Euroimmun, Luebeck) using serial dilutions until the immunofluorescence reactivity was no longer visible. CSF and serum samples have been evaluated by two independent observers. The CSF sample of February 2015 resulted positive until the dilution of 1:50; CSF sample of June was positive until the titer of 1:5 and the CSF sample of March until the dilution of 1:4 (Fig. 1). Anti-NMDAR antibodies were absent in serum at all time points.

CSF samples in the acute stage and during the follow-up in patients with anti-NMDAR encephalitis have been analyzed in few reports [3–5]. In a previous study, the authors reported that CSF and serum titers are higher in patients with poor outcome and in patients with tumors, suggesting that tumor

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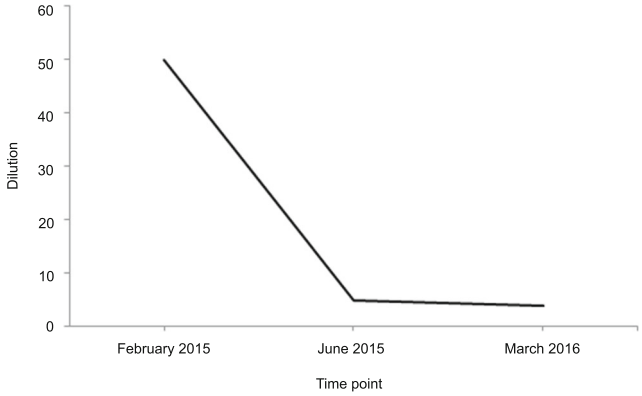


**Fig. 1** Analysis of undiluted CSF showed the presence of anti-NMDAR antibodies both in the acute phase and in the follow-up. However, antibody reactivity persisted until the CSF was diluted of 1:50 only in early stages of the disease. In June 2015 and March 2016, anti-NMDAR antibodies were detectable until the CSF dilution of 1:5 and 1:4, respectively, confirming a decrease in antibody titer over time

may represent a trigger of the immune response. Moreover, titers decrease slowly during the follow-up, but earlier in the CSF of patients with good outcome, suggesting that CSF detection of specific antibodies is a reliable prognostic marker [2]. In the case reported here, the presence of anti-NMDAR antibodies in the CSF, but not in the serum, suggests that the teratoma could contribute in breaking the immune tolerance, but other factors may be involved too. The immune response to preceding flu-like syndrome might have facilitated the crossing of the blood-brain barrier. However, the detection of antibodies only in the CSF suggests that intrathecal synthesis is crucial for the maintenance of the intrathecal immune response. Here, the pathogenic role of the antibodies is confirmed by the correlation between antibody titers and neurological outcome as shown by the rapid decrease of the titer after recovery and by the further slight reduction of their levels during the follow-up. However, the persistence of CSF antibodies even after the complete recovery suggests that the presence of anti-NMDAR antibodies is a necessary but not sufficient condition to the onset of symptomatic encephalitis. According to literature, anti-NMDAR antibodies target the same epitope region in all patients, regardless of their outcome [2]. Therefore, in the case reported here, the good outcome despite the presence of anti-NMDAR antibodies in the CSF might underline the role of the immune tolerance and the possible presence of neutralizing antibodies rather that a modification in antibodies' conformation. The reduction of the antibody titer during the follow-up highlights the role of the antibodies threshold, probably associated with other factors, in inducing a clinically relevant syndrome.

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**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest.

**Informed consent** Informed consent was obtained from the patient described in this report.

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