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LETTER TO THE EDITORS

Paraneoplastic anti-NMDAR encephalitis: long term follow-up reveals persistent serum antibodies

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Dear Sirs,

Encephalitis associated with antibodies to *N*-methyl-D-aspartate receptor (NMDAR) is a severe but treatable condition [3]. It is often paraneoplastic, affecting mostly women harboring ovarian teratomas. Its characteristic clinical picture includes confusion, agitation, psychiatric manifestations, memory loss, seizures and abnormal movements, and often leads to decreased level of consciousness, autonomic instability, and central hypoventilation [1, 5]. We present the long term follow-up of a patient with paraneoplastic anti-NMDAR encephalitis diagnosed several months after symptom onset who was in a comatose state for 1 year. A prolonged recovery followed after tumor resection and immunotherapy. Two notable observations are the absence of a detectable tumor at an early stage of the disease, and the persistent detection of serum NMDAR antibodies 4 years after disease onset.

A 42-year-old woman suffering from headaches 2 months before disease onset, was admitted to an Athens hospital with neck pain, nausea, dizziness and high fever. She was alert and oriented. Her initial work up (brain and spinal MRI, chest and abdominal CT, routine laboratory tests) was normal. Lumbar puncture revealed pleiocytosis (421 lymphocytes/mm^3) but no oligoclonal bands. CSF and serum cultures for bacterial, fungal and viral infections were negative.

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Two days after admission she became delusional with visual hallucinations, confusion, central hypoventilation and a progressive consciousness decline that led to a coma requiring ventilation 10 days after admission. Her EEG was slowing, disorganized, with no basic rhythm but without epileptic foci. The initial diagnosis was viral encephalitis with non convulsive status epilepticus and she was treated with antibiotics, antivirals and antiepileptics. Her condition worsened with episodes of hyperpyrexia, agitation, orofacial dyskinesias, stiffness, and seemingly violent movements of her upper arms. These episodes diminished significantly with dantrolene. A transvaginal echo was normal. She was treated with steroids and one course of IVIg but she remained unresponsive. In ICU the patient had multiple episodes of septicemia but she responded well to therapy. Seven months after disease onset she was transferred to our institution in a comatose state with tracheostomy and gastrostomy.

Repeated CSF analysis for bacterial and viral infections was negative. Other systemic autoimmune causes were excluded and all autoantibody tests were negative (ANA, Ro, La, cANCA, pANCA, rheumatoid factor). Brain MRI was normal. An upper and lower abdominal MRI (looking for ovarian tumors) was negative. A suspected immune mediated encephalitis was treated with IVIg infusions, 2 g/kg/36 h per month. A month later (month 9 from disease onset), a CT re-examination of the lower abdomen revealed a cystic formation at the left ovary. Following resection, pathology revealed a mature ovarian teratoma. NMDAR autoantibodies were detected in the serum and CSF using a qualitative assay (Fig. 1a).

The patient started to communicate 40 days after tumor resection. IVIg infusions continued monthly for 7 months and she continued to improve slowly. No steroids, cyclophosphamide or plasmapheresis were added due to

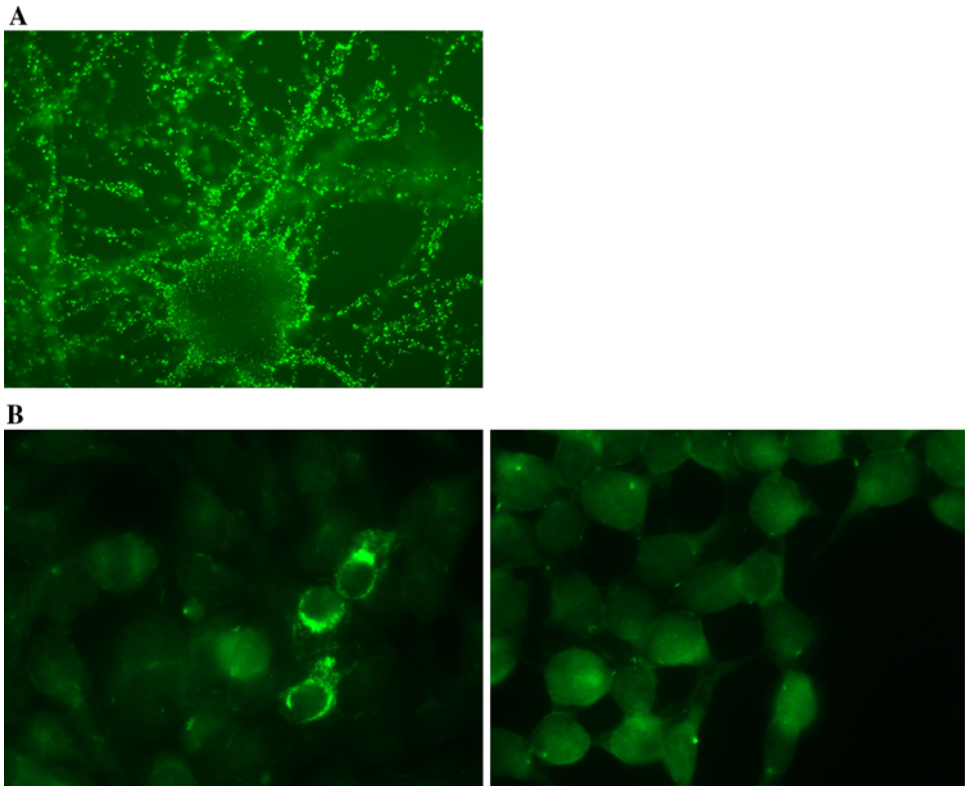

Fig. 1 **a** Patient sera and CSF was tested on cultured hippocampal neurons which express NMDA receptors on their surface. Positive staining (serum) was observed confirming the presence of anti-NMDAR antibodies. **b** Patient sera, obtained 4 years after symptoms onset was tested against human embryonic kidney (HEK) cells expressing NMDAR on their surface (Euroimmun). Positive staining was observed (*left*) confirming the continuing presence of autoantibodies. No staining was observed in untransfected HEK cells (*right*)

previous multiple episodes of septicemia. As she was coming out of the coma, she exhibited multiple episodes of agitation and confusion requiring risperidone. She slowly became more alert and after 2 years her cognitive function improved and she was discharged.

The patient slowly became ambulatory with a residual mild cognitive dysfunction which was noticeably improving every 6 months while receiving Aricept. She became able to recall some details of her hospitalization and resume some of her work duties. Re-testing for NMDAR autoantibodies using a cell-based assay (Fig. 1b), revealed persistence of serum antibodies. CSF was not re-tested. The two antibody assays were done in two different laboratories. Unfortunately, for practical reasons, the antibody titers could not be re-checked simultaneously by the same laboratory. The patient died suddenly from an apparent heart attack while on a cruise vacation.

Encephalitis associated with NMDAR autoantibodies due to ovarian teratoma is an increasingly common paraneoplastic autoimmune disorder. If diagnosed early and treated promptly it can be reversible. Often, the cause is overlooked and treatment is substantially delayed leading to a prolonged coma, permanent disability or death [2]. Our case highlights a number of important observations. First, the need to persist with all available imaging tools for the search of the ovarian tumor if the syndrome is clinically suspected. In our patient, transvaginal echo and abdominal MRI early on were negative but eventually the CT scan revealed the tumor almost a year later. This is not uncommon in other paraneoplastic syndromes. Second, persistence of immunotherapy combined with tumor resection can be effective even a year later, while further improvement of cognitive function can slowly continue even 4 years from disease onset. Third, in spite of clinical improvement and normal brain imaging, serum antibodies persisted even after 4 years. In a series of four Japanese patients, no antibodies to NMDAR were found after 4–7 years of follow-up [4]. Although the syndrome appears to be driven by intrathecally produced antibodies, the persistence of serum antibodies in the context of substantial clinical recovery is of interest. It is unclear whether these antibodies had a long-lasting effect on the CNS resulting in residual mild neurological deficits. An alternative explanation is that the residual dysfunction was due to neuronal damage caused by the antibodies owing to delay in treatment initiation or complications during disease course (e.g., seizures, infections, sepsis). Some B cell clones may persist in the peripheral lymphoid tissue and remain able to trigger an immune relapse. Whether in such patients B cell depletion therapy will be helpful, remains uncertain.

All human studies have been approved by the Faculty of Medicine, University of Athens Ethics Committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Conflict of interest Dr. Alexopoulos reports no conflict of interest. Dr. Kosmidis reports no conflict of interest. Dr. Dalmau receives research support from Euroimmun and the NIH/NCI (RO1CA107192 [PI] and RO1CA89054-06A2 [PI]); has received license fee payments from Euroimmun for a patent re: NMDA receptor autoantibody test; and has received royalty payments and may accrue revenue for a patent re: Ma2 autoantibody test. Dr. Dalakas reports no conflict of interest.

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