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LETTER TO THE EDITOR

Anti-NMDA receptor encephalitis possibly triggered by measles virus

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Introduction

Anti-NMDA receptor encephalitis and variant disorders are serious, yet treatable diseases in which antibodies formed in response to a number of possible stimuli (i.e., tumor, infection, etc.) cross-react with synaptic proteins, most commonly the *N*-methyl-D-aspartate receptor (NMDAR) [1]. We present a case of anti-NMDA-R encephalitis associated with positive measles virus serology.

Case report

A 29-year-old woman with no previous medical history was admitted in our department in October 2012 with behavioral disturbance that started insidiously with apathy 15 days ago. She was first seen by a psychiatrist who referred her for neurologic evaluation. Neurological examination showed mixed aphasia, bilateral horizontal nystagmus, positive palmomental reflex and right Babinski sign. Routine blood counts, chemistries and CSF cytochemistry provided normal findings. However, CSF electrophoresis revealed oligoclonal bands, while serum immunological workup was positive for measles antibodies, IgG 3000 and IgM 1.54 Au/ml. Interestingly, the corresponding CSF titer for measles IgG was 170 Au/ml and negative for IgM. The patient was also tested and found negative for other viruses such as herpes simplex, zoster, varicella, cytomegalovirus, HIV, coxsackie, echo and hepatitis. She had no history of measles infection and she had been vaccinated earlier in her life. She had also not been exposed to anyone suffering from measles in the preceding few days or months. At the same time brain MRI and CT scan of the chest and abdomen were all normal.

During hospitalization the patient presented generalized tonic–clonic seizures which were controlled with intravenous phenytoin. Electroencephalography (EEG) demonstrated paroxysmal slow polymorphic activity in the left fronto-temporal region. Several other laboratory studies, including serum anti-Hu, Yo, Ri, anti-Ma2, CV2 as well as serum and CSF anti-amphiphysin, VGCK, NMDA receptor antibodies were all either normal or negative. The patient received a 5-day course of 1000 mg/day methylprednisolone intravenously (iv), her speech improved and remained free of seizures.

In mid-November 2012 repeat serum immunoglobulins for measles virus was positive; however, with decreased titer for IgG (700 Au/ml) and negative IgM antibodies. On discharge, she was given oral phenytoin (300 mg/day) and prednisolone 60 mg/day with dose tapering. On regular clinical and EEG follow-up the patient had complete recovery in speech and behavior, she remained without seizures and in view of normal EEG recordings antiepileptic treatment was discontinued in February 2013. Nevertheless, in August she was readmitted for generalized tonic–clonic seizure. Neurologic examination and a second brain MRI were normal and the patient was discharged on oral levetiracetam (2000 mg/d).

Three months later, in November 2013, the epilepsy recurred, this time as simple as well as complex partial seizures. Antiepileptic treatment with oral levetiracetam (2000 mg/day) and carbamazepine (1600 mg/day) was given and the patient received a second 5-day course of 1000 mg/day methylprednisolone (iv).

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At that time a new CSF sample was negative for measles antibodies and serum search demonstrated further decrease in the IgG titer for the virus (22.29 Au/ml) and negative IgM. Additionally, a repeat serology and CSF search for different autoimmune encephalopathies was normal; nevertheless, this time the patient was found positive for anti-NMDA receptor antibodies both in the serum (1:640) and CSF (1:160). Subsequent ovarian CT scan was also normal. A final serum and CSF investigation for NMDA antibodies in March 2014 was positive in both samples; however, with decreased titers (serum 1:160, CSF 1:40). The patient remains on oral antiepileptic and steroid treatment (initially prednisolone 60 mg/day with tapering) and is free of symptoms and signs on regular follow-up until today.

Discussion

The core feature of our case was the behavioral presentation that needed initial psychiatric consultation. Anti-NMDA-R encephalitis could present with behavioral changes, apathy or psychosis that start insidiously [2]. Measles encephalitis occurs from direct viral-induced cellular damage or from immune-mediated tissue damage [3]. In our case, the stepwise reduction of measles antibodies in the serum and the absence of IgM in CSF, in combination with no overt clinical signs of recent infection argues against a true measles encephalitis. The brain complications of measles are all severe and can appear within days or years of acute infection [4]. In this context, we speculate that measles virus triggered anti-NMDA-R encephalitis and this is compatible with the reduction of measles antibodies that could be detectable for a long period of time. On the other hand, CSF abnormalities are initially present in 80 % of patients with anti-NMDA-R encephalitis and the remaining of them are negative, as happened in our case.

In this sense, measles virus antibodies without a clear measles infection could have triggered anti-NMDA-R encephalitis from the beginning, but we were unable to document it because of negative antibodies initially, although behavioral problems and epilepsy are the core features in the majority of patients with anti-NMDA-R encephalitis [2].

Additionally, other immune-mediated disorders that are associated with B cell dysregulation and could present fluctuations in measles IgG titers in the absence of active disease, were ruled out, such as multiple sclerosis or the clinically isolated syndrome [5].

The response to steroids and the relapse after steroid discontinuation is another paradigm for the autoimmune process. Although there are reports suggesting that herpes simplex virus can trigger anti-NMDA-R encephalitis [6], to our knowledge there is no report implicating measles virus. Whether this post-infectious entity is caused by mechanisms of mimicry or breakdown of immunological tolerance towards the NMDAR antibodies expressed by damaged neurons is unknown [1]. Albeit uncommon, we should consider testing patients for immune-mediated encephalitis, in cases with atypical presentations or with relapses of viral origin.

Conflict of interest We state that there is no conflict of interest.

Ethical standard All human and animal studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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