

Autoimmune Encephalitis With mGluR1 Antibodies Presenting With Epilepsy, but Without Cerebellar Signs

A Case Report

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Abstract

Objective

To describe the unique case history of a patient with mGluR1 antibodies, with mainly limbic and without cerebellar symptoms.

Methods

A 50-year-old woman initially presented with focal seizures with epigastric rising and déjà-vu sensations, next to cognitive complaints, and musical auditory hallucinations. MRI, EEG, and neuronal autoantibody tests were performed.

Results

EEG findings showed slow and sharp activity (sharp waves and sharp-wave–slow-wave complex) in the left temporal lobe. A test for autoantibodies was negative initially. Because of persistent symptoms, serum and CSF were tested 4 years later and found positive for mGluR1 antibodies. Treatment started with monthly IV immunoglobulins and azathioprine that was replaced by mycophenolate mofetil later. Especially cognitive symptoms and hallucinations did not respond well to the treatment. During treatment, mGluR1 antibodies remained present in CSF.

Discussion

Whereas cerebellar symptoms are present in 97% of mGluR1-positive cases, our patient presented without ataxia. Therefore, we suggest that the clinical presentation of patients with mGluR1 antibodies is probably more diverse than previously described. Testing for mGluR1 antibodies should be considered in patients with limbic encephalitis and epilepsy, especially when negative for more common antibodies.

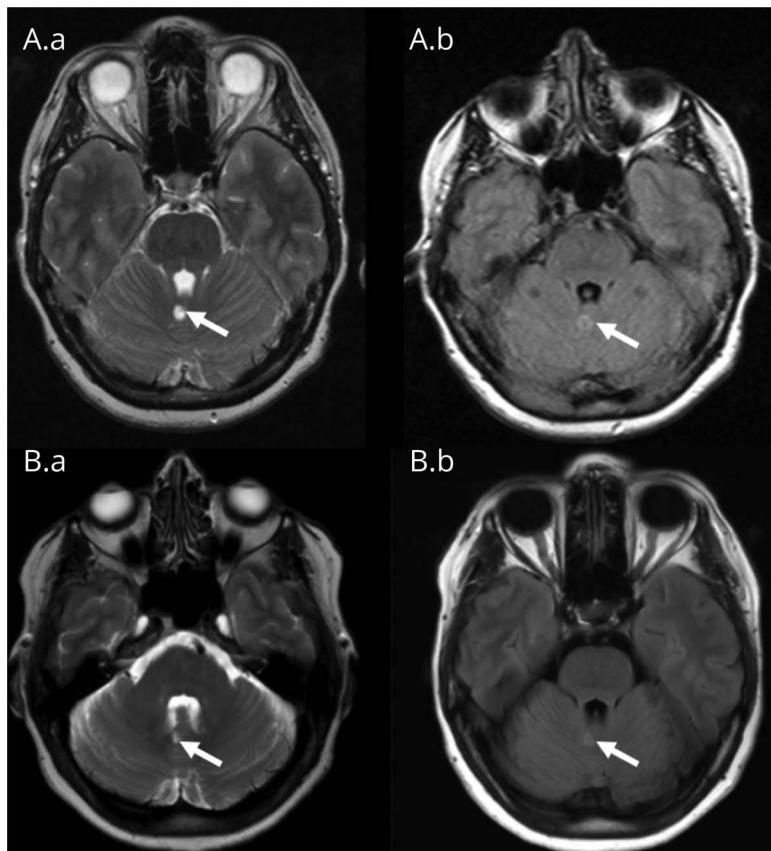
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(A.a-b) MRI of the brain (A.a: axial T2-weighted image; A.b: axial fluid-attenuated inversion recovery [FLAIR] image) shortly after the first presentation. The arrow shows the spot of increased signal intensity in the cerebellar vermis caused by vascular damage. (B.a-b) An MRI examination of the brain performed recently (4 years after symptom onset) shows no progression of the cerebellar lesion or any other abnormal findings.

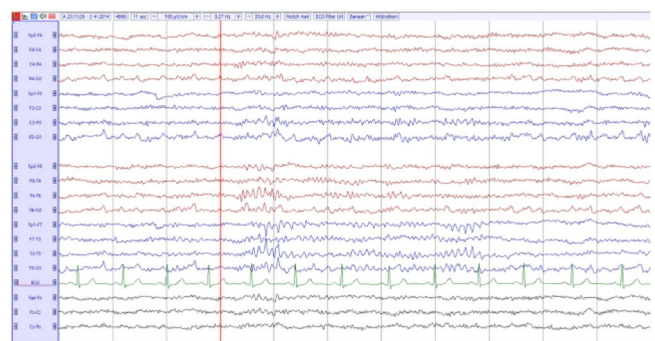
A 50-year-old woman, with a history of vasovagal syncope, cardiac ablation, and migraine, presented with an episode of acute distress and confusion, screaming and crying, followed by stuttering speech and vomiting. The patient was unable to recall this incident.

For several weeks, she had experienced a mild headache and episodes of musical hallucinations, lasting for hours. Moreover, the patient experienced multiple episodes of epigastric rising and déjà-vu sensations. There were no abnormalities in the physical and neurologic examinations and in routine blood tests and the ECG. An MRI examination of the brain showed 2 nonrecent vascular lesions, one in the vermis (Figure 1) and the other in the right frontal cortex. An EEG showed slow and sharp activity (sharp waves and sharp-wave–slow-wave complex) in the left temporal lobe (Figure 2). Symptoms and findings were consistent with focal epilepsy, with focal seizures with a sensory onset and intact awareness and one focal seizure with impaired awareness. After these findings, the patient started using lamotrigine and later, clobazam. In the etiologic workup, the CSF recurrently showed slight pleocytosis (6–10 leucocytes/ μL), 100% mononuclear, and unique oligoclonal IgG bands. However, anti-GAD65 was absent in serum by ELISA (RSR Limited, Cardiff, UK).

Tapering off antiepileptic drugs resulted in recurring focal seizures with sensory onset, 18 months after the first

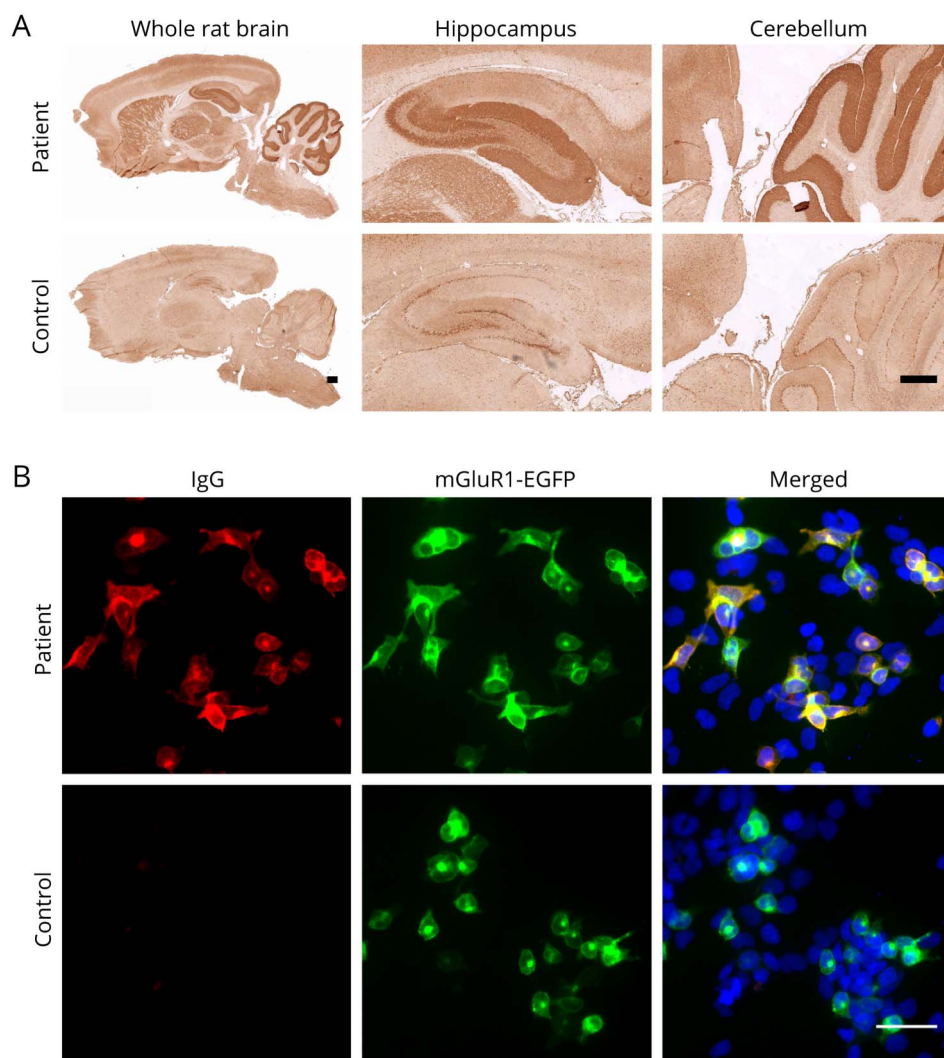
presentation. Then, she was treated with valproic acid with good response. However, no treatment reduced her auditory hallucinations. Furthermore, she experienced cognitive problems since the onset of symptoms. Formal neuropsychological testing showed reduced processing speed and a slight degree of word-finding difficulties, without prominent aphasia.

Figure 2 Electro-Encephalogram



The electro-encephalogram (EEG) 6 months after initial presentation. It shows a normal background pattern, with a focal abnormality (sometimes with epileptiform features) in the left (more than in the right) temporal lobe. These abnormalities did not have a clinical correlate.

Figure 3 Immunohistochemistry on Rat Brain and Live Neuron Stainings



(A) Tissue-based assay: serum from the patient showed strong reactivity on rat brain compared with that from a negative control. The reactivity was mainly in the CA3 area and dentate gyrus area of hippocampus and the molecular layer of cerebellum. Scale bar = 500 μ m. (B) Cell-based assay: Serum from this patient showed clear staining on transfected cells compared with serum from a healthy individual, which did not show any IgG staining to the transfected cells. mGluR1-enhanced green fluorescent protein (EGFP) transfected human embryonic kidney (HEK) cells were used for the staining (green). IgG autoantibodies were stained with goat anti-human IgG 594 (red, #109-546-170, Jackson), and nuclei were stained with 4',6-diamidino-2'-phenylindole dihydrochloride (DAPI) (blue). Scale bar = 50 μ m.

Because of the unclear etiology, we retested the serum taken initially, 48 months after the first test for autoantibodies, using immunohistochemistry (IHC),¹ which resulted in staining with mGluR1 pattern (Figure 3A).² We confirmed this with a cell-based assay (CBA) (Figure 3B).² Newly collected CSF was tested and proved strongly positive for anti-mGluR1. The serum showed negative results, which suggested intrathecal production of anti-mGluR1 antibodies. Serum and CSF samples, tested for other neuronal autoantibodies, were all negative (including in-house CBA for GAD65/67, mGluR5, and a commercial CBA testing kit: autoimmune encephalitis Mosaic 1, Euroimmun, Lübeck, Germany).

After the exclusion of a primary tumor causing the antibody production by total body CT/PET scan, the patient was treated with IV immunoglobulin (IVIG) (a monthly recurring course of 0.4 mg/kg/d IVIG for 5 consecutive days, for 5 months, in a tapering schedule). Maintenance therapy was started with azathioprine, which was later replaced by

mycophenolate mofetil because of an increase in hallucinations. During therapy, the patient experienced improvement of her well-being, with more energy and less memory problems. Besides, the musical hallucinations were less frequent. However, over the last years, the patient had experienced relapsing episodes with an increase in musical hallucinations, headache, and fatigue. A repeated MRI examination of the brain showed no changes. Moreover, an EEG finding showed no electroencephalographic correlate for the musical hallucinations. Based on these findings, mycophenolate mofetil and valproic acid were continued. Throughout the disease history, the CSF remained positive for anti-mGluR1, even after treatment (CSF collected 67 months after initial clinical presentation).

Discussion

We found mGluR1 antibodies in a patient with the classic triad for limbic encephalitis (epilepsy and psychiatric and

cognitive complaints), whereas previous studies reported ataxia as the most predominant symptom, occurring in 97% in a series of patients with mGluR1 antibodies.³ mGluR1 is not only highly expressed in Purkinje cell dendrites of the cerebellar cortex but also present in neurons located in the thalamus, hippocampus, globus pallidus, substantia nigra, deep nuclei of the cerebellum, and superior colliculus.⁴ The reason why our patient showed no signs of cerebellar involvement remains to be determined.

Our patient experienced only a partial and temporary improvement after the immunomodulatory therapy, which might be due to the long delay between start of the symptoms and start of immunomodulatory treatment.⁵ Another possible explanation could be the inability of most commonly used immune treatments to result in a rapid and sustained control of the immune response within the CNS.⁶ The delay of treatment could have been prevented because our patient had an antibodies contributing to focal epilepsy signs and symptoms (ACES) score of 2, which relates to a higher chance of an autoimmune cause for her epilepsy.⁷ Furthermore, IHC shows its advantage as a supplementary method for screening, whereas antibody screening in clinical practice by several specific CBA has its limitations.

In conclusion, presentation of anti-mGluR1-related disease can be more diverse than previously believed. Testing for mGluR1 antibodies should be considered in patients with limbic encephalitis and epilepsy, especially when negative for more common antibodies.

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Appendix (continued)

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