Metabotropic Glutamate Receptor Type 1 Autoantibody–Associated Cerebellitis

A Primary Autoimmune Disease?

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Objectives: To report the third case of subacute cerebellar ataxia associated with metabotropic glutamate receptor type 1 autoantibodies (mGluR1-Abs), an uncommon syndrome known to be part of the group of paraneoplastic cerebellar degeneration syndromes linked to antineuronal antibodies and previously reported in only 2 other patients with long-term remission of Hodgkin lymphoma, and to discuss the underlying immunopathogenesis.

Design: Case report.

Setting: University hospital.

Patient: A 50-year-old woman admitted for acute severe isolated static and kinetic cerebellar syndrome. Magnetic resonance imaging of the brain showed diffuse abnormal hyperintensity in the whole cerebellum on fluid-attenuated inversion recovery and diffusion sequences.

Results: Results of the biological workup were negative for general inflammation, vitamin deficiency, and bacterial and viral infections. Immunohistochemical analysis of the serum and cerebrospinal fluid of the patient demonstrated staining for Purkinje cell bodies and the molecular layer of the cerebellum. Finally, mGluR1-Abs were detected in serum and cerebrospinal fluid by a cell-based assay. Complete clinical examination, thoracoabdominal-pelvic computed tomography, and whole-body fludeoxyglucose F 18–positron emission tomography failed to show any underlying tumor, including Hodgkin lymphoma. The disease was stabilized after a course of intravenous immunoglobulins and continuous mycophenolate mofetil treatment during a follow-up of 40 months.

Conclusions: Cerebellitis associated with mGluR1-Abs should be considered in the differential diagnosis of patients with subacute cerebellar ataxia. This first case without any tumor found suggests a possible idiopathic autoimmune rather than a paraneoplastic mechanism. In consideration of this possible primitive autoimmune ataxia involving the directly pathogenic mGluR1-Abs, immunosuppressive therapy should be initiated as early as possible.

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We report the third case of isolated subacute cerebellar ataxia associated with mGluR1-Abs. The disease has been stabilized after a course of intravenous immunoglobulin therapy and continuous mycophenolate mofetil treatment. To our knowledge, this is the first case with no evidence of cancer after a follow-up of 40 months.

A 50-year-old female dancer without a remarkable medical history was admitted to our department in March 2006 for severe balance and gait disturbances, dysarthria, and oscillopsia, which developed during a period of 4 days. She also reported diffuse transient headache in the preceding days. No evidence of infection or toxic exposure was found.
At clinical examination, the patient’s mental status was normal. The patient was unable to walk or sit alone. Head titubation and truncal sway were present while sitting. Static and kinetic cerebellar syndromes were patent, with bilateral dysmetria in both arms and legs. Oculomotor examination showed intense vertical nystagmus and diminution in the speed of horizontal and vertical saccades. No motor or sensory deficit was present. There was no clinical evidence of an underlying tumor. Magnetic resonance imaging (MRI) of the brain showed diffuse abnormal hypointensity in the whole cerebellum on fluid-attenuated inversion recovery and diffusion sequences (Figure, A), with no abnormalities on T1-weighted (Figure, B), T1-weighted gadolinium-enhanced, and T2-weighted images. Magnetic resonance angiography was normal. Results of the biological workup were negative for general inflammation, vitamin deficiency, and bacterial or viral infections. Analysis of the cerebrospinal fluid (CSF) showed pleocytosis (190/mm³ with a lymphocyte predominance), elevated protein level (72 mg/dL [to convert to grams per liter, multiply by 0.01]), glucose level and IgG index (0.6) within the reference ranges, and no oligoclonal IgG bands. Based on the MRI and CSF analysis results, a wide-spectrum anti-infectious treatment for possible infectious cerebellitis was started. However, CSF cultures were negative for bacterial or fungal infections, and polymerase chain reaction found no evidence of herpesvirus family infection. Consequently, anti-infectious drug therapy was stopped after 10 days. No clinical improvement was observed during this period. For detecting onconeural antibodies, indirect immunocytchemistry was performed on rat brain sections. It demonstrated staining for Purkinje cell bodies and the molecular layer of the cerebellum using the serum and CSF of the patient (screening dilution for serum, 1:20 000; for CSF, 1:500) (Figure, E). The pattern of labeling was different from that seen with anti-Tr antibodies. In addition, the serum of the patient did not inhibit the immunostaining of a biotinylated anti-Tr IgG. Results of Western blotting using onconeural recombinant proteins (Hu, Yo, Ri, CV2, amphiphysin, Ma2, and Homer 3) were negative. Finally, mGluR1-Abs were detected in the serum and CSF by means of abolishment of the typical staining pattern on sections of mGluR1-knockout mice, as previously described (not shown). To confirm the mGluR1 specificity of these antibodies, a cell-based assay was developed. Briefly, the coding sequence of mouse mGluR1 was cloned in a green fluorescent protein expression vector (GeneCopoeia, Rockville, Maryland). For the cell-based assay, human embryonic kidney cells (HEK293) were grown on glass coverslips in Dulbecco modified Eagle medium (Gibco, Grand Island, New York) with 10% fetal calf serum. After 24 hours, cells were transfected using a transfection reagent (Lipofectamine LTX; Invitrogen, Cergy-Pontoise, France) with the mGluR1 green fluorescent protein–tagged expression construct. Twenty-four hours after transfection, the cells were fixed with 4% paraformaldehyde for 10 minutes and then incubated in a saturation buffer (phosphate-buffered saline, 0.2% gelatin and 0.01% Triton). Cells were then incubated with the patient’s CSF (1:50) for 90 minutes. Cells were subsequently washed in phosphate-buffered saline and then incubated with Cy3-conjugated antihuman IgG. The CSF of the patient was positive for mGluR1 antibody, whereas CSF samples from 10 patients with other cerebellar degeneration (2 with anti–glutamic acid decarboxylase antibodies, 2 with anti-Tr antibodies, 1 with anti-Yo antibodies, and 5 without known antibodies) were negative for mGluR1 antibody on the mGluR1 cell-based assay (Figure 1F-H). Results of whole-body computed tomography, fluoroxyglucose F 18 (18F)–positron emission tomography, and mammograms were normal. Serum β2–microglobulin and lactic dehydrogenase assays and bone marrow aspiration yielded negative findings.

Three weeks after the clinical onset of the disease, a course of intravenous immunoglobulins, 2 g per kilogram of body weight, was administered across 5 days, and a continuous treatment with mycophenolate mofetil, 2 g/d, and oral prednisone, 1 mg/kg per day, was started. Three months later, the patient showed a progressive clinical improvement with less severe dysarthria and head titubation. Abnormalities detected in diffusion sequences of MRI had decreased, and a moderate cerebellar atrophy could be visualized on T1-weighted sequences (Figure, C and D). The anti–mGluR1-Ab serum titer had dropped to 1:500. Tapering of the corticosteroid therapy led to cessation of the corticosteroid therapy 8 months later; the mycophenolate mofetil therapy was continued.

At the last visit 40 months after the onset of the cerebellitis, while still taking mycophenolate mofetil, 2 g/d, as the only treatment, the patient still had a static and kinetic cerebellar syndrome but was able to walk with aid. Speech had dramatically improved. Brain MRI was stable with a persistent mild cerebellar atrophy. Anti–mGluR1-Abs were persistent in the serum but at a low titer (1:500). The complete clinical examination, thoracoabdominal-pelvic computed tomography, and whole-body 18F–positron emission tomography scan failed to show any underlying tumor, including Hodgkin lymphoma.

We report the third case of cerebellitis associated with anti–mGluR1-Abs found in serum and CSF. An initial MRI of the brain showed diffuse hyperintense signals of the cerebellum on fluid-attenuated inversion recovery and diffusion sequences. Therapy with intravenous immunoglobulins, corticosteroids, and mycophenolate mofetil improved the cerebellar dysfunction. To our knowledge, this is the first case without any tumor found after a 40-month follow-up, suggesting a possible idiopathic autoimmune rather than paraneoplastic mechanism.

Paraneoplastic cerebellar degeneration is defined as a subacute onset of cerebellar dysfunction in patients with cancer that is not explained by known causes. Many patients with PCD harbor partially or well-characterized antineuronal antibodies. The pathogenesis of PCD remains unknown but is thought to be an immune-mediated cytotoxic T-lymphocyte response that contributes to the degeneration of Purkinje cells. Onconeural antibodies against cytoplasmic or nuclear antigens expressed intracellularly in the tumor and neurons are important for diagnosis but do not appear to be directly pathogenetic.
Antibodies against mGluR1 were previously identified in only 2 patients, who developed cerebellar ataxia with normal brain MRI findings after remission of Hodgkin lymphoma for 2 and 9 years. They were therefore considered to be a rare cause of PCD associated with partially characterized onconeural antibodies. Similar to what

Figure. Evaluation of metabotropic glutamate receptor type 1 autoantibody (mGluR1-Ab)–associated cerebellitis. A, Diffuse hypersignal of the cerebellum on axial diffusion sequences (arrow) in March 2006 (initial examination). B, No abnormality on T1-weighted sequences at the same time. C, Diffusion abnormalities have disappeared by September 2006. D, Moderate cerebellar atrophy on the sagittal T1-weighted sequence. E, Specific staining of the Purkinje cells and molecular layer using indirect immunofluorescence on slices of rat cerebellum (original magnification ×200). G indicates granular layer; M, molecular layer; and P, Purkinje cells (arrow). F-H, Cell-based assay with human embryonic kidney (HEK293) cells transfected with the mGluR1–green fluorescent protein (GFP) tagged expression construct. F, GFP staining. G, Cy3-conjugated antihuman IgG staining. With serum from the patient, GFP staining and Cy3-conjugated antihuman IgG staining perfectly match. H, Staining with 4′,6′-diamidino-2-phenylindole dichloride confirms the cellular-specific staining.
is currently described in neuromuscular junction syndromes and anti-\(N\)-methyl-\(D\)-aspartate receptor encephalitis,\(^8\) mGlur1-Abs, found in the serum and CSF, are considered directly pathogenic. Indeed, mGlur1 is a cell-surface receptor abundantly present at the presynaptic site of the Purkinje cell dendritic spines in the cerebellum. Blocking this receptor in mice leads to characteristic cerebellar symptoms with impaired cerebellar long-term depression and impaired motor learning.\(^9\) Thus, its activation seems to be necessary for normal motor coordination.\(^10\),\(^11\) Moreover, the passive transfer of mGlur1 antibodies into the cerebellar arachnoid space of mice causes severe and reversible ataxia.\(^2\)

In the 2 initial patients and as acknowledged by the authors,\(^2\) the paraneoplastic link between the Hodgkin lymphoma and mGlur1-Abs remains elusive because of the long interval between the cancer and the ataxia onset. Furthermore, no expression of mGlur1 was detected in tumoral lymph nodes. In our case, clinical examinations and imaging did not show any underlying tumor after 40 months of follow-up. A primitive autoimmune mechanism involving mGlur1-Abs can therefore be hypothesized. In the 2 original cases, this autoimmune mechanism may have been induced by the Hodgkin lymphoma itself or by the chemotherapy used.

Treatment of paraneoplastic neurological syndromes associated with antineuronal antibodies is challenging, often with poor outcomes despite empirical immunological therapies.\(^12\) In our case, considering a possible primitive autoimmune ataxia involving antibodies against mGlur1, we initially used intravenous immunoglobulins and corticosteroid treatment. Mycophenolate mofetil, which inhibits the proliferative responses of T and B lymphocytes and antibody production by B lymphocytes,\(^13\) was used from the beginning and pursued as a maintenance therapy. We believe that this strategy allowed partial control of the cerebellar symptoms, limited the cerebellar atrophy, and possibly prevented further relapses. However, a spontaneously remitting monophasic autoimmune process cannot be dismissed. In any case, such an immunoactive intervention, which could also incorporate plasma exchanges, should be initiated as early as possible before complete irreversible cerebellar damage occurs. Presumably, the intensity and duration of the immunosuppressive maintenance therapy might be adapted according to the evolution of the antibodies against mGlur1, knowing that effective therapy can transform the mGlur1-Abs to a negative status.\(^2\)

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