ARTICLE

Encephalitis with mGluR5 antibodies

Symptoms and antibody effects

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Abstract

Objective

To report the clinical features of 11 patients with metabotropic glutamate receptor 5 (mGluR5) antibody–associated encephalitis, immunoglobulin G (IgG) subclass, and effects of the antibodies on neuronal mGluR5 clusters.

Methods

Clinical information was retrospectively obtained from referring physicians. Antibodies to mGluR5 and IgG subclasses were determined with brain immunohistochemistry and cell-based assays. The effects of the antibodies were examined on rat hippocampal neurons with reported techniques.

Results

From January 2005 to May 2017, 11 patients (median age 29 years, range 6–75 years, 5 female) were identified. The main clinical features were psychiatric (10), cognitive (10), movement disorders (7), sleep dysfunction (7), and seizures (6). Median modified Rankin Scale score at the peak of the disease was 4; 4 patients required intensive care. Five patients had Hodgkin lymphoma, and 1 had small cell lung cancer. CSF showed pleocytosis (median white blood cell count 22 mm^3) in all patients; brain MRI was abnormal in 5, involving limbic (1) or extralimbic (4) regions. Treatments included immunotherapy and/or oncologic therapy; at the last follow-up (median 48 months), 6 patients had complete and 5 had partial recovery. Neurologic relapse occurred in 2 patients. Antibodies were IgG1 alone (4 of 9) or in combination with IgG2 (1 of 9), IgG3 (3 of 9), or both (1). Patients' IgG caused a significant and specific decrease of cell-surface synaptic and extrasynaptic mGluR5 without altering the levels of postsynaptic density protein 95.

Conclusions

Anti-mGluR5 encephalitis associates with a complex neuropsychiatric syndrome, not restricted to limbic encephalitis, and can occur without tumor. Patients respond to treatment, but relapses can occur. The antibodies have pathogenic effects altering the levels of cell-surface mGluR5.

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Glossary

AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; **CBA** = cell-based assay; **$GABA_AR$** = $GABA_A$ receptor; **$GABA_BR$** = $GABA_B$ receptor; **GluR** = glutamate receptor; **IgG** = immunoglobulin G; **iGluR** = ionotropic glutamate receptor; **HEK** = human embryonic kidney; **mGluR** = metabotropic glutamate receptor; **mRS** = modified Rankin Scale; **NMDAR** = NMDA receptor; **PSD95** = postsynaptic density protein 95.

Glutamate receptors (GluRs) are the main mediators of excitatory synaptic transmission in the brain.[1] Dysfunction of these receptors has been related to several psychiatric, neurodevelopmental, or neurodegenerative disorders such as schizophrenia, autism, Parkinson disease, and Huntington disease.[2–4] GluRs can be classified as ionotropic (iGluRs), which act as glutamate-gated ion channels, and metabotropic receptors (mGluRs), which are coupled to G proteins and activate intracellular signaling.[5] In the last decade, iGluRs and mGluRs have been identified as targets of antibodies in a number of well-characterized autoimmune neurologic disorders. The clinical syndromes associated with iGluRs antibodies include, for example, anti-NMDA receptor (NMDAR) encephalitis, which manifests with psychosis, cognitive decline, movement disorders, dysautonomia, and coma,[6,7] or the less frequent anti–α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) limbic encephalitis, which associates with short-term memory loss, confusion, and seizures.[8,9] For these disorders, there is substantial evidence that the antibodies are pathogenic.[10,11] As far as the mGluRs are concerned, there is evidence that mGluR1 antibodies associate with cerebellar dysfunction[12–15]; however, the clinical features and comorbid conditions of mGluR5 antibodies have been reported in only 4 patients, and the effects of the antibodies are unknown.[16–18] In the current study, we report 7 additional patients with mGluR5 antibody–associated encephalitis and the pathogenic effects of the antibodies.

Methods

Identification of patients, sample collection, and clinical information

Between January 2005 and May 2017, we investigated the sera or CSF of 14,475 patients with various neurologic disorders (including autoimmune encephalitis, classic paraneoplastic syndromes, neurodegenerative diseases, demyelinating disorders, prion diseases, peripheral neuropathies, viral encephalitis), whose samples had been sent for neuronal antibody studies. All samples were screened for reactivity against rat brain neuropil by immunohistochemistry and cell-based assays (CBAs) for NMDAR, as previously reported.[6,9] In case of positive neuropil reactivity different from that of NMDAR antibodies, samples were then investigated with CBA for antibodies to mGluR5 and other neuronal targets (AMPAR, $GABA_B$ receptor [$GABA_BR$], $GABA_A$ receptor [$GABA_AR$], LGI1, CASPR2, DPPX, GlyR, GAD65, IgLON5, dopamine2 receptor, neurexin-3α, and mGluR1) with previously reported techniques.[6,9,19–24] In addition, all patients samples were routinely screened for classic onconeuronal antibodies.

Clinical information was either obtained by the investigators or retrieved from questionnaires completed by the referring clinicians and included prodromal symptoms, neurologic manifestations, comorbidities, results of ancillary studies, and immunotherapy and cancer treatment. Symptom severity was measured with the modified Rankin Scale (mRS)[25] at the peak of the disease and the last follow-up. Outcome was classified as complete recovery (if patients returned to their baseline condition), partial recovery (if patients had significant improvement but were not back to their baseline condition), lack of improvement, or death. Four patients have been previously published,[16–18] and we obtained the long-term follow-up since the initial reports. Samples from 3 of these patients were available for immunoglobulin G (IgG) subclass studies.

mGluR5 CBA, IgG subclass, and confocal microscopy studies on cultured neurons

Details of the mGluR5 CBA, determination of patients' IgG subclasses, and study of antibody effects on cultured neurons are provided in the supplemental information (links.lww.com/WNL/A492). Briefly, human embryonic kidney (HEK) cells were transfected with mGluR5 and treated with patients' serum or CSF. Reactivity was analyzed by immunofluorescence with secondary antibodies against total IgG or specific for IgG subclasses (IgG1, IgG2, IgG3, IgG4). IgG purified from the serum of patient 3 and a healthy participant were used for experiments examining the effect of patient's antibodies or control IgG on total cell-surface and synaptic mGluR5 clusters. The mGluR5 specificity of the patient's purified IgG was confirmed with immunoabsorption studies. The antibody effects were then studied with fetal rat hippocampal neurons incubated for 24 hours with the patient's purified IgG or control IgG (80 μg/mL media). In addition, the process of recovery was examined by removing the antibodies from the media and determining the density of receptors after 48 hours, 96 hours, and 7 days. Cell-surface mGluR5 receptors were visualized by immunofluorescence and quantified by confocal imaging (LSM710, Carl Zeiss, Jena, Germany) and Imaris suite 7.6.4 (Bitplane AG, Zürich, Switzerland).

Standard protocol approvals, registrations and patient consents

This study was approved by the Institutional Review Board of the Hospital Clinic (Barcelona, Spain). All patients gave

written informed consent for use of samples and clinical information.

Statistical analyses

Statistical analyses and graphing were performed with GraphPad Prism, Excel, and STATA. The comparison of clinical variables between adults and children was performed with the 2-tailed Fisher exact test and Mann-Whitney *U* test, whereas the effects of antibodies on mGluR5 and postsynaptic density protein 95 (PSD95) cluster density were assessed with 2-way analysis of variance and Bonferroni correction for multiple test comparison. Results with values of $p < 0.05$ were regarded as statistically significant.

Data availability

Any data not published within the article are available and will be shared anonymized by request from any qualified investigator.

Results

Clinical features and antibody studies

Eleven patients with anti-mGluR5 encephalitis were identified. Clinical information, results from ancillary tests, treatment, and outcome at last follow-up are detailed in the table. Median age was 29 (range 6–75, interquartile range [15–46]) years, including 4 children <18 years of age and 7 adults. Median duration of symptoms by the time of diagnosis was 1.75 (0.25–48) months. An association with tumors or other autoimmune conditions occurred in 7 patients: 5 had Hodgkin lymphoma, 1 had small cell lung cancer, and 1 had Crohn disease. In all 6 patients with tumor, the neurologic disorder preceded the tumor diagnosis by 2 to 11 months. Nine patients had prodromal symptoms such as headache (6), weight loss (3, all with tumor), nausea (2), erythema/rash (2), or upper respiratory tract infection (1). Four patients had fever, either preceding (1) or during (3) the neurologic symptoms. The most frequent neurologic manifestations were behavior or personality/mood changes (10 of 11, 91%), ranging from irritability or agitation to severe anxiety, depression, and full-blown psychosis with abnormal thought processes and hallucinations; altered cognition (10 of 11, 91%), including deficits in memory, attention, visuospatial, and executive functions; sleep disturbances (7 of 11, 64%), with increased (3) or decreased (4) sleep duration or poor quality sleep; seizures (6 of 11, 55%), manifesting as status epilepticus in 2; decreased level of consciousness (6 of 11, 55%); and movement disorders (5 of 11, 45%), including myoclonus and postural tremor in 2 adults, orofacial dyskinesias in 1 adult, and dystonia in 2 children. The adult with small cell lung cancer, who also had SOX1 antibodies, had an atypical presentation with progressive external ophthalmoplegia, limb hypertonia, postural tremor, gait instability, and executive dysfunction. At the peak of the disease, which occurred after a median of 2 weeks from symptom onset, patients had a median mRS score of 4.0 (range 3–5), and 4 of 11 (36%) patients required intensive care (median stay 5, range 4–12 days) because of pharmacologically induced coma for status epilepticus (2), extreme agitation (1), or renal failure (1).

All patients showed CSF pleocytosis (median 25, range 6–114 white blood cells/mm^3), and 6 of 8 (75%) had oligoclonal bands. EEG was abnormal in 5 of 10 (50%) patients, showing focal or diffuse slowing, and was associated with epileptiform discharges in 2 (both children) with clinically manifested seizures. Diffuse slowing was observed more frequently in children than adults (3 of 4 vs 0 of 6, $p < 0.05$). Brain MRI T2/fluid-attenuated inversion recovery abnormalities were found in 5 of 11 (45%) patients and involved limbic (1) or extralimbic (3) regions such as thalamus, pons, frontal or parieto-occipital cortex, cerebellum, or both (1). Brain fluorodeoxyglucose-PET was performed in 3 patients and showed severely decreased metabolism of the temporoparietal cortex (2) or cerebellum (1), with normal brain MRI in 2 of them.

Among the 6 patients with tumor, 4 received first-line immunotherapy (corticosteroids, plasmapheresis, IV immunoglobulins) and cancer treatment, and 2 received only cancer treatment. Among the 5 patients without tumor, 4 received first-line immunotherapy followed in 2 by second-line immunotherapy (rituximab), and 1 patient received no immunotherapy. At the last follow-up (median 48 months), all patients showed recovery that was complete (6) or partial (5), with a median mRS score of 0. Patient 3, without tumor, and patient 6, with Hodgkin lymphoma, experienced neurologic relapse (30 and 16 months after the first episode, respectively), which in patient 6 preceded a tumor relapse by 5 months. In both patients, treatment of the relapse with immunotherapy (and cancer treatment, including brentuximab and autologous stem cell transplantation) resulted in significant improvement of neurologic symptoms.

Serum or CSF was available from all patients (5 paired samples, 3 CSF alone, and 3 serum alone). Antibodies to mGluR5 were found in serum and CSF of all paired samples. The main IgG subclass of mGluR5 antibodies was IgG1, which was found in 9 of 9 patients, either alone (4) or associated with IgG2 (1), IgG3 (3), or both IgG2 and IgG3 (1). None of the patients harbored IgG4 antibodies (figure 1). All patients' samples were negative for classic onconeuronal antibodies.

Study of antibody effects on hippocampal cultured neurons

Purified patient's IgG and IgG from a healthy blood donor (control) were used for these experiments. The mGluR5 specificity of purified patient's IgG was confirmed with immunoabsorption studies (figure 2). Compared with control IgG, incubation with patient IgG for 24 hours caused a significant decrease of both total (figure 3, A and C) and synaptic (figure 3D) cell-surface mGluR5 clusters without affecting the density of PSD95 clusters, which is a synaptic marker (figure 3A and figure e-1, links.lww.com/WNL/A491). A similar effect on mGluR5 protein, but not on AMPAR protein, was observed

Table Main clinical features, antibody titers, and IgG subclasses in 11 patients with anti-mGluR5 encephalitis

Patient, sex, age, y	Prodromal features	Tumor	Main clinical features; mRS score at peak of disease	CSF analysis	Increased T2/FLAIR signal on MRI	Treatment	Last follow-up, mo; outcome; mRS score	Ab titer; IgG subclass
Patient 1[a], F, 46	None	HD, stage 3A	Personality changes and depression for 1 y, then seizures, memory loss, emotional lability, myoclonic jerks, and tremor. mRS score 3	23 WBC	At onset: unilateral right mesiotemporal lobe. At 3 mo: bilateral temporal, thalamus, insula, frontal. Gd+	Steroids, AVBD	48; Complete recovery; mRS score 0	S: +; CSF: NA
Patient 2[a], M, 35	Weight loss (9 kg)	HD, stage 2B	Aggressive behavior, depressed mood and anxiety, memory loss, right X and XII nerve palsy. mRS score 3	12 WBC	Bilateral (right > left) upper pons. Gd+	AVBD	38; Complete recovery; mRS score 0	S: NA; CSF: 1/160; IgG1
Patient 3[a], F, 30	Weight loss (22 kg), flu-like symptoms	None	Personality change, aggressive behavior, hypersomnia, memory loss, visuospatial deficit, prosopagnosia, dLOC, seizures. mRS score 3. Relapse at 16 mo. mRS score 2	25 WBC, OCB	Normal	Steroids, PE, RTX	48; Mild residual attention deficit; mRS score 1	S: 1/1280; CSF: 1/320; IgG1, IgG3
Patient 4, M, 75	Weight loss (11 kg)	SCLC	Progressive ophthalmoplegia, postural hand tremor, gait instability, executive dysfunction. mRS score 4	6 WBC, increased IgG index	Bilateral mesiotemporal lobes	Steroids, IVIg, chemotherapy, RT	62; Improved cognition, ophthalmoplegia unchanged; mRS score 3	S: 1/160; CSF: 1/320; IgG1
Patient 5, F, 40	Headache	None	Insomnia, anxiety, psychosis, auditory hallucinations, memory loss, dLOC, akinetic mutism, orofacial dyskinesia. mRS score 5	45 WBC	Normal	Steroids, PE	20; Complete recovery; mRS score 0	S>>1/1280; CSF: NA; IgG1
Patient 6, M, 16	Headache	HD, stage 3B	Psychosis, hallucinations, poor sleep, dystonia, generalized seizures, dLOC. mRS score 4. After complete recovery, neurologic relapse followed by tumor relapse	31 WBC, OCB	Normal	Steroids, chemotherapy, PE	48; Complete recovery; mRS score 0	S: >>1/1280; CSF: 1/20; IgG1, IgG3
Patient 7, F, 6	Rash, headache, flu-like symptoms	None	Status epilepticus, dLOC, aphasia, memory loss, poor sleep with altered sleep-wake cycle, followed by dystonia and oculogyric crisis, psychomotor slowness, ataxia, speech and motor regression, hypoventilation. mRS score 5	21 WBC, OCB negative	Bilateral frontal (left > right) and right occipital lobes, cerebellum	Steroids, IVIg, RTX	19; Partial, improved aphasia, cannot walk unassisted; mRS score 3	S: NA; CSF: 1/10; IgG1

Continued

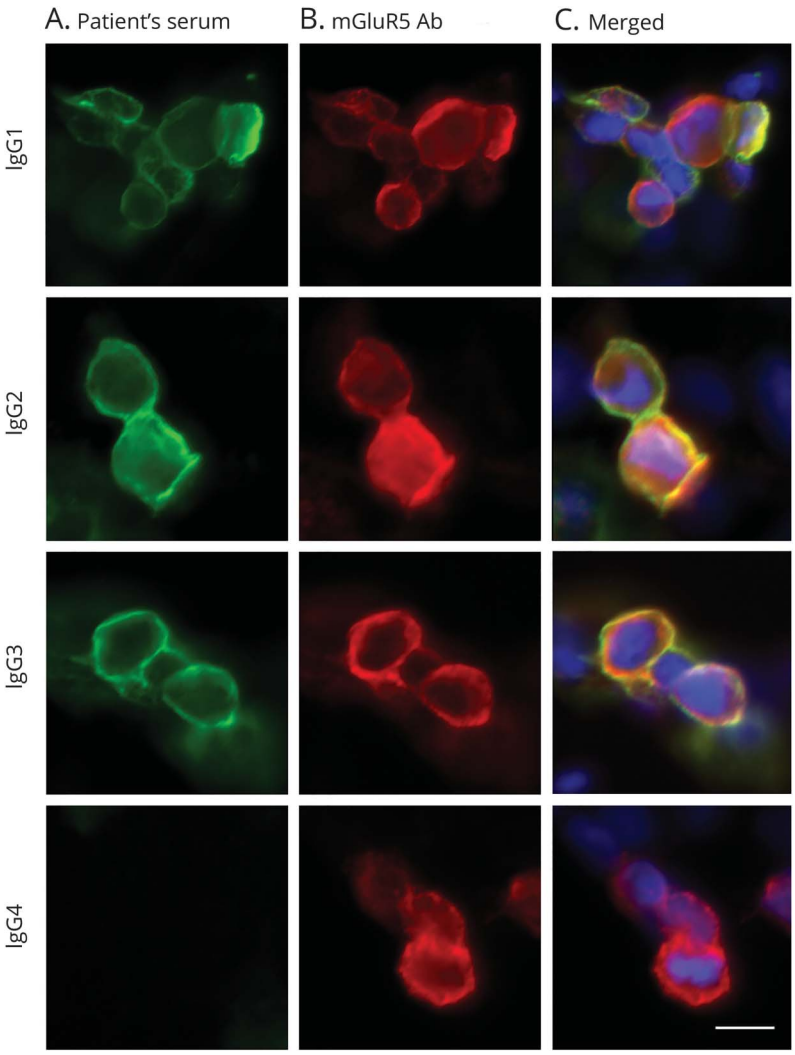
Table Main clinical features, antibody titers, and IgG subclasses in 11 patients with anti-mGluR5 encephalitis *(continued)*

Patient, sex, age, y	Prodromal features	Tumor	Main clinical features; mRS score at peak of disease	CSF analysis	Increased T2/FLAIR signal on MRI	Treatment	Last follow-up, mo; outcome; mRS score	Ab titer; IgG subclass
Patient 8[a], M, 15	Headache, nausea	HD, stage 2A	Confusion, auditory and visual hallucinations, decreased verbal output, attention deficit, status epilepticus. mRS score 5	114 WBC, OCB	Bilateral (left > right) posterior cortical diffusion restriction	Chemotherapy, RT	72; Complete recovery; mRS score 0	S: NA; CSF: +++
Patient 9, F, 20	Headache, flu-like symptoms	None	Psychosis, emotional lability, thought disorder, anterograde amnesia, psychomotor slowing, hypersomnia. mRS score 4	27 WBC, OCB	Normal	None	96; Complete recovery; mRS score 0	S: >>1/1280; CSF: NA; IgG1, IgG2
Patient 10, M, 15	None	HD stage 1	Facial paralysis, then developed altered behavior, memory loss, anxiety, irritability, visual hallucinations, insomnia. mRS score 4	45 WBC, OCB	Normal	Steroids, IVIg, chemotherapy	12; Moderate memory problems; mRS score 2	S: 1/1280; CSF: 1/640; IgG1, IgG2, IgG3
Patient 11, M, 49	None	None	Insomnia, altered behavior, mania, emotional lability, psychomotor agitation, dLOC, seizures. mRS score 4	75 WBC, OCB	Normal	Steroids	5; Mild verbal memory and executive deficits; mRS score 1	S: 1/320; CSF: 1/160; IgG1, IgG3

Abbreviations: Ab = antibody; AVBD = chemotherapy with doxorubicin, vinblastine, bleomycin, and dacarbazine; dLOC = decreased level of consciousness; FLAIR = fluid-attenuated inversion recovery; Gd+ = gadolinium enhancement; HD = Hodgkin disease; IgG = immunoglobulin G; IVIg = IV immunoglobulin; mGluR5 = metabotropic glutamate receptor 5; mRS = modified Rankin Scale; NA = not available; OCB = CSF oligoclonal bands; PE = plasma exchange; RT = radiotherapy; RTX = rituximab; SCLC = small cell lung cancer; WBC = white blood cells per mm^3; +/+++ = sample positive/strongly positive for mGluR5 cell-based assay but not available for antibody titer determination and IgG subclass study.

[a] Four published cases: patients 1 and 8, Lancaster et al.[16]; patient 2, Mat et al.[17]; and patient 3, Prüss et al.[18]

Figure 1 IgG subclass of patient's mGluR5 antibodies



Serum of a representative patient (patient 10) showing reactivity (green; A) with human embryonic kidney cells expressing metabotropic glutamate receptor 5 (mGluR5); the colocalization of reactivity with a commercial antibody against mGluR5 (red; B) is shown in the merged images (yellow; C). This patient had mGluR5 antibodies (Abs) of immunoglobulin G1 (IgG1), IgG2, and IgG3, but not IgG4, subclasses. Scale bar 10 μm.

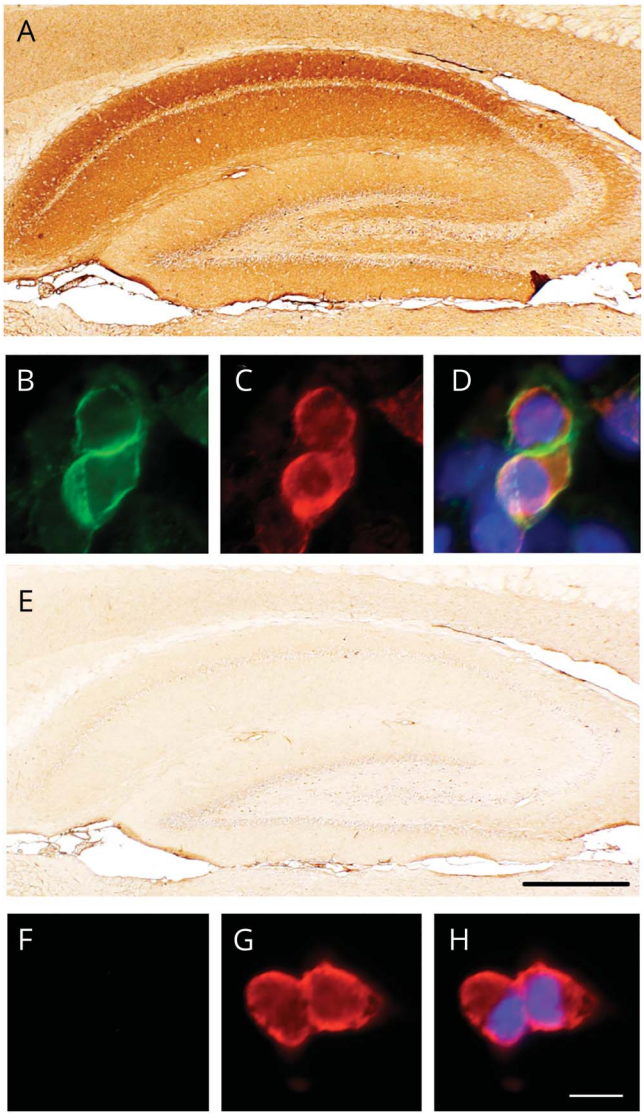
in immunoblot analysis of cell-surface biotinylated proteins after 24 hours of treatment with the patient's IgG (figure 3B). These effects were reversible; the levels of mGluR5 clusters were progressively restored after neurons were allowed to recover without the patient's IgG. Recovery was first noted 96 hours after removal of the antibodies, and the mGluR5 levels were back to baseline 7 days after antibody removal (figure 3D).

Discussion

The current study confirms and expands the phenotype previously reported in 4 patients with mGluR5 antibody–related encephalitis[16–18] and shows that the antibodies specifically decrease the levels of cell-surface mGluR5 but not other synaptic proteins such as PSD95 or AMPAR.

The occurrence of mGluR5 autoantibodies was initially reported in 2 young patients with Ophelia syndrome,[16] which refers to encephalitis with psychosis, memory deficits, and dreamy state, associated with Hodgkin lymphoma.[26] In our current study, most patients had a prodromal viral-like phase followed by development of prominent psychiatric features, ranging from emotional lability, anxiety, or depression to full-blown psychosis with hallucinations, along with personality and behavioral changes and memory and cognitive dysfunction. In more than half of the patients, these symptoms occurred in association with seizures, movement disorders, altered level of consciousness, and sleep disturbances, including poor sleep quality or quantity, or hypersomnia. Although anti-mGluR5 encephalitis has been often considered a form of limbic encephalitis,[16,18] these clinical features suggest a wider involvement of brain structures outside the limbic system, as supported by the observation that in 4 of 5 patients with abnormal MRI, the brain abnormalities were not restricted to the mesiotemporal lobes but also involved the parieto-occipital cortex, thalamus, pons, and cerebellum. None of the patients showed the pattern of extensive multifocal fluid-attenuated inversion recovery cortical and

Figure 2 Abrogation of patient's serum reactivity with rat brain after immunoabsorption with HEK cells expressing mGluR5



The reactivity of patient's serum with rat brain, shown in (A), and with human embryonic kidney (HEK) cells expressing metabotropic glutamate receptor 5 (mGluR5), shown in (B), is abolished (E and F) after the serum has been immunoabsorbed with HEK cells expressing mGluR5. Panels (C and G) correspond to HEK cells incubated with a commercial mGluR5 antibody, and panels (D and H) correspond to the colocalization of the reactivities (patient's and commercial antibody). Scale bar: rat brain = 2 mm; HEK cells = 10 μm.

subcortical MRI abnormalities that characterizes anti-$GABA_AR$ encephalitis.[22]

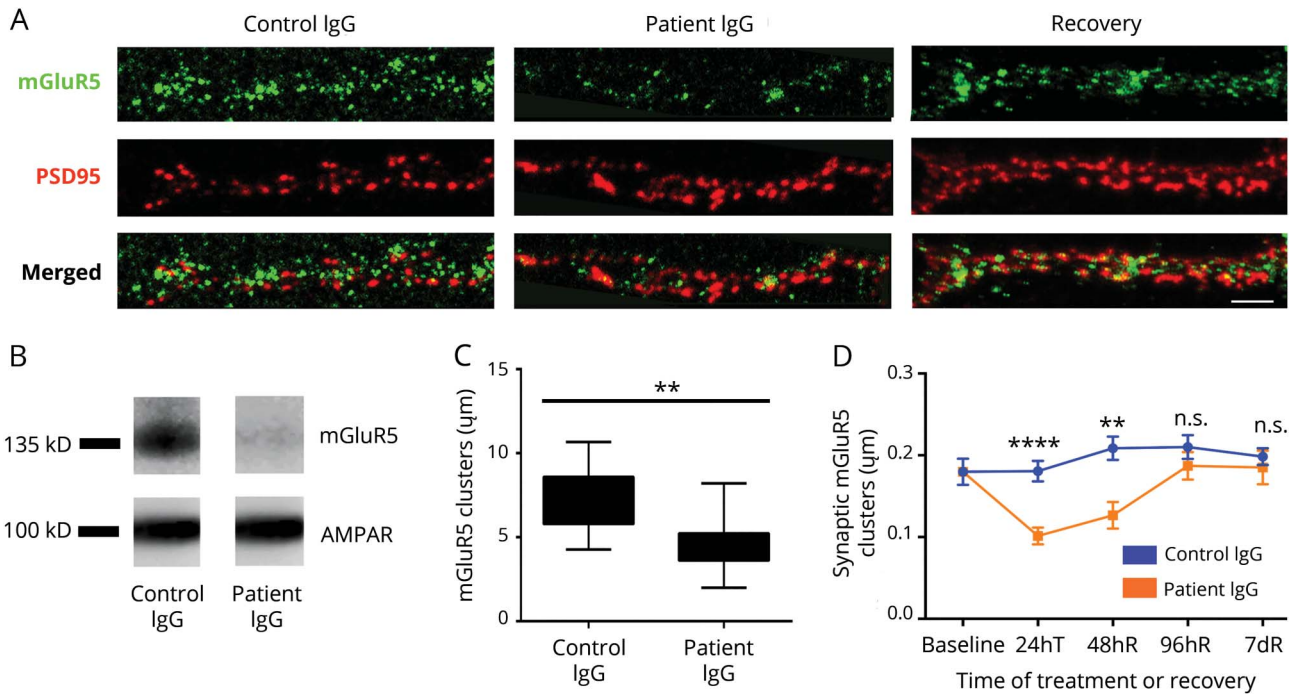
One finding is that anti-mGluR5 encephalitis can occur with tumors other than Hodgkin lymphoma such as small cell lung cancer, which in our patient associated with atypical clinical manifestations, including progressive bilateral ophthalmoplegia. Moreover, in almost half of the patients, the disorder was not paraneoplastic, as suggested by a previous case report.[18] Our study shows that anti-mGluR5 encephalitis often affects young adults but can also occur in school-aged children and in the elderly. In children, movement disorders included dystonic postures and oculogyric crisis, whereas in adults they manifested as postural tremor or myoclonic jerks. One young woman showed transient orofacial dyskinesias, although they were less prominent and persistent than those observed in anti-NMDAR encephalitis. Compared with adults, children had only generalized seizures and were more prone to develop status epilepticus and to show diffuse slowing on the EEG ($p < 0.05$). This age-dependent difference in clinical manifestations is not unique to anti-mGluR5 encephalitis; it has also been observed in encephalitis associated with NMDAR or $GABA_AR$ antibodies[22,27] and might be related to an increased susceptibility to develop seizures or a higher vulnerability of some brain structures during neurodevelopment such as the basal ganglia and hippocampus.

Anti-mGluR5 encephalitis seems to be a rare disorder. However, the idea that this autoimmune response is closely related to the presence of a Hodgkin lymphoma may contribute to its underrecognition. If this were the case, 45% of our patients (without evidence of a tumor) would not have been suspected to have this disorder. In addition, testing for mGluR5 antibodies is currently not included in commercial panels.

Recognition of anti-mGluR5 encephalitis is clinically relevant given the excellent response to immunotherapy and cancer treatment, if needed. Indeed, although patients were severely ill and 36% of them required intensive care management, all showed complete or partial recovery at the last follow-up. Our study shows that neurologic relapses can occur, and therefore, patients should be followed up closely. This is important because the response to immunotherapy at relapse was as good as at the first episode and because the neurologic relapse may herald tumor recurrence, as occurred in one of our patients.

Patients' antibodies caused a significant decrease of mGluR5 cluster density, at both synaptic and extrasynaptic locations, without disrupting the PSD95 cluster density or altering the levels of AMPAR protein. These effects were reversible after removing the antibodies from the media, with complete recovery of receptor density over 7 days. Together with the good response to immunotherapy and cancer treatment (if needed) in most patients, these data suggest a pathogenic role of the antibodies most likely unrelated to complement- or cell-mediated cytotoxicity, which would probably cause less reversible deficits. However, the exact mechanism by which the antibodies alter receptor density is still unknown. Given our observation that the antibodies are of the IgG1 subclass, it is likely that they may cross-link and internalize the receptors, similar to the effects reported for IgG1 against ionotropic NMDAR or AMPAR.[10,28] A task for the future is determine these mechanisms in vitro and in animal models, which might

Figure 3 Patient's antibodies cause a specific decrease of density of cell-surface mGluR5 clusters in cultured neurons



Representative confocal images (from 40 dendrites per condition) showing a decrease of density of cell-surface metabotropic glutamate receptor 5 (mGluR5) clusters in neurons treated for 24 hours with patient's immunoglobulin G (IgG) compared with neurons treated with control IgG (A). Quantification analysis of total mGluR5 clusters after 24 hours of treatment is shown in panel (C). Specific decrease of mGluR5 protein, but not α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) protein, is also demonstrated using immunoblot of biotinylated neuronal membrane fractions from neurons treated for 24 hours with patient's IgG compared to control IgG (B). These effects were reversible, and baseline levels of total (A, right column, 7 days recovery) and synaptic (D) neuronal cell-surface mGluR5 clusters (from analysis of 20 dendrites per condition per time point) were progressively restored over 96 hours to 7 days. Statistical analyses by 2-way analysis of variance; mean and SEM are plotted. Scale bar = 10 µm. $^{**}p < 0.05$, $^{****}p < 0.0001$. PSD95 = postsynaptic density protein 95; R = recovery; T = treatment.

improve the understanding of other neurologic and psychiatric disorders related to mGluR5 dysfunction such as Fragile X syndrome and others.[2–4,29–31]

Author contributions

Design/conceptualization of the study, analysis and interpretation of the data: M.S., L.S., E.M.-H., and J.D. Data collection: M.S., L.S., E.M.-H., T.A., T.I., R.L., H.P., E.M.O., N.H., N.T., R.L.C.O., J.-C.A., F.G., J.D. Statistical analysis: M. S. Figure development: M.S., L.S., J.P., J.D. Drafting of the manuscript: M.S., M.R.R., F.G., J.D.

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Disclosure

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Encephalitis with mGluR5 antibodies

Symptoms and antibody effects

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Study questions

What are the clinical features and response to treatment of patients with metabotropic glutamate receptor 5 (mGluR5)-antibody-associated encephalitis? Which is the main IgG subclass and what are the effects of mGluR5 antibodies on neuronal mGluR5 clusters?

Summary answer

Anti-mGluR5 encephalitis associates with a complex neuropsychiatric syndrome, not restricted to limbic encephalitis, and can occur without tumor association. Patients respond to immunotherapy although relapses can occur. The antibodies are mainly IgG1 and IgG3 and have pathogenic effects altering the levels of cell surface mGluR5.

What is known and what this paper adds

Anti-mGluR5 encephalitis has been reported in a few patients with new onset of memory problems, psychosis and Hodgkin's lymphoma (Ophelia syndrome). This study allows better characterization of clinical manifestations, tumor association (beyond Hodgkin lymphoma), CSF analysis and brain MRI, and long-term outcome of patients with this disorder. The study also provides evidence of the pathogenicity of mGluR5 antibodies.

Participants and setting

Patients with anti-mGluR5 encephalitis were identified from 14,475 patients with various neurologic disorders whose samples were sent for neuronal antibody studies to Hospital Clinic, University of Barcelona, between January 2005 and May 2017.

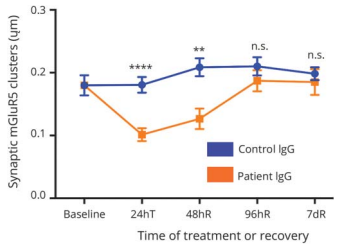
Design, size, and duration

Clinical information was retrospectively obtained from referring physicians. Antibodies to mGluR5 and IgG subclasses were determined using brain immunohistochemistry and in-house cell-based assays. The effects of the antibodies on the clusters of cell-surface mGluR5 and the synaptic marker PSD95 were determined on live rat hippocampal neurons with confocal imaging and quantitation analysis.

Main results and the role of chance

Eleven patients (median age 29 years, 5 female) were identified. The main clinical features were psychiatric (10), cognitive (10), movement disorders (7), sleep dysfunction (7), and seizures (6). Median modified Rankin Scale at the peak of the disease was 4, and 4 patients required intensive care. Five patients had Hodgkin lymphoma, and 1 small-cell lung cancer. CSF showed pleocytosis (median WBC 22) in all patients; brain MRI was abnormal in 5, involving limbic (1) or extra-limbic regions (4). Treatments included immunotherapy or oncologic therapy; at the last follow-up (median, 48 months) 6 patients had complete and 5 partial recovery. Neurologic relapse occurred in 2 patients. Antibodies were IgG1 alone (4/9) or in combination with IgG2 (1/9), IgG3 (3/9) or both (1). Patients' IgG caused a specific decrease of cell-surface synaptic and extrasynaptic mGluR5 without altering PSD95 (figure).

Figure Patients' antibodies cause a decrease of synaptic mGluR5



Decrease of synaptic cell-surface mGluR5 clusters in neurons treated for 24 hours with patient's IgG (orange line) compared with neurons treated with control IgG (blue line). $^{**}p < 0.05$, $^{****}p < 0.0001$. n.s. = not statistically significant.

Bias, confounding, and other reasons for caution

The number of patients is small. This study used an in-house cell-based assay to determine mGluR5 antibodies, which is currently not included in commercial panels.

Generalizability to other populations

Although anti-mGluR5 encephalitis is regarded as a rare disorder, the idea that this autoimmune encephalitis is closely related to the presence of a Hodgkin lymphoma may contribute to its under-recognition. If this was the case, 45% of the reported patients (without evidence of a tumor) would not have been suspected to have this disorder.

Study funding/potential competing interests

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A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.

