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Autoimmune encephalitis associated with antibodies against the metabotropic glutamate receptor type 1: case report and review of the literature

Monika Christ, Torsten Müller, Corinna Bien, Thomas Hagen, Markus Naumann and Antonios Bayas

Abstract: Autoimmune encephalitis associated with antibodies against the metabotropic glutamate receptor type 1 is a rare autoimmune disease with only 18 cases being described in the literature so far. Most patients present with subacute cerebellar ataxia. In more than one third of cases a paraneoplastic aetiology has been suspected. Here we report a case of a 45-year-old man without known malignancy, who presented with progressive dysarthria and subsequently developed subacute cerebellar ataxia. Immunotherapy with glucocorticoids, i.v. immunoglobulins and rituximab improved clinical symptoms and resulted in a stable disease course up to the present. The article describes the clinical course of the patient with a follow-up-period of approximately 24 months and reviews the cases reported in the literature so far.

Keywords: ataxia, autoimmune encephalitis, dysarthria, metabotropic glutamate receptor type 1

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Introduction

The increasing number of encephalitis-associated antibodies discovered in the past few years has steadily provoked clinical and scientific interest in autoimmune encephalitis. A position paper has recently defined diagnostic criteria based on clinical symptoms to facilitate the early diagnosis and therapy of autoimmune encephalitis.[1] Accordingly, a possible autoimmune encephalitis can be diagnosed in subjects with subacute onset (⩽ 3 months) of memory deficit, psychiatric symptoms or impaired mental status, if alternative causes are excluded and if at least one of the following criteria is fulfilled: focal neurological signs, new seizures, magnetic resonance imaging (MRI) abnormalities suggestive of encephalitis or cerebrospinal fluid (CSF) pleocytosis.[1] However, not all patients with autoimmune encephalitis meet these criteria, most notably at the early stage of the disease.[2] The definitive diagnosis requires the detection of specific antibodies. Initiation of immunotherapy early in the disease course is crucial for the prognosis in proven autoimmune encephalitis.[3] First-line therapy consists of intravenous (i.v.) glucocorticoids, i.v. immunoglobulins (IVIG) and plasma exchange or immunoadsorption; second-line therapeutics include rituximab and cyclophosphamide.[4]

Metabotropic glutamate receptor type 1 (mGluR1) is a G protein-coupled cell-surface receptor[5] that is strongly expressed in the Purkinje cell dendrites of the cerebellar cortex in particular, but is also present in cells of the olfactory bulb, neurons located in the thalamus, hippocampus, globus pallidus, substantia nigra, deep nuclei of the cerebellum and superior colliculus.[6–10] In the cerebellum, mGluR1 mediates long-term depression of fibres parallel to Purkinje cells and therefore plays an essential role in cerebellar motor learning and coordination.[11,12]

Autoantibodies against mGluR1 cause a rare form of autoimmune encephalitis primarily leading to subacute cerebellar ataxia.[13–19] So far, only 18 cases have been described in the literature. In addition to cerebellar ataxia, a variable spectrum

Correspondence to:
Monika Christ
Department of Neurology, University Hospital of Augsburg, Stenglinstraße 2, D-86156 Augsburg, Germany
monika.christ@uk-augsburg.de

Torsten Müller
NeuroZentrum am Königsplatz, Augsburg, Germany

Corinna Bien
Laboratory Krone, Bad Salzuflen, Germany

Thomas Hagen
Radiology Center, Augsburg, Germany

Markus Naumann
Antonios Bayas
Department of Neurology, University Hospital of Augsburg, Augsburg, Germany

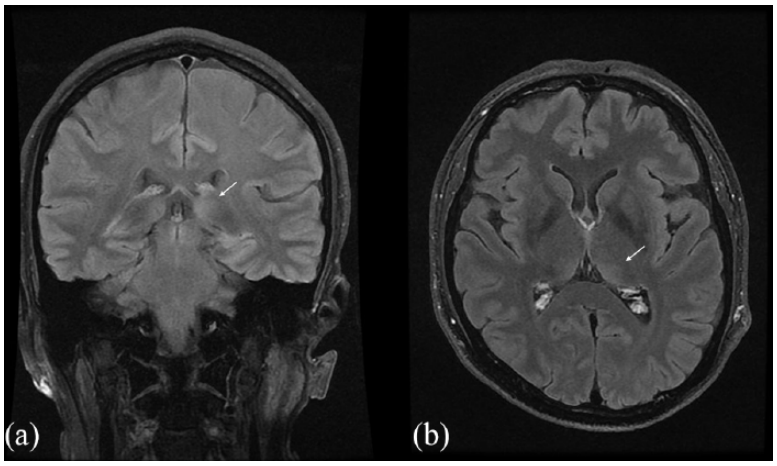

Figure 1. MRI fluid-attenuated inversion recovery (FLAIR) images: (a) coronal, August 2016; (b) axial, April 2017 with abnormal hyperintensity in the thalamus and pulvinar predominantly on the left.

of symptoms (e.g. dysarthria, head titubation, cognitive impairment, dysgeusia, etc.) has been described.[13–19]

The transfer of purified anti-mGluR1 immunoglobulin G (IgG) of affected patients to cerebellar slices of mice resulted in disturbed excitability, plasticity and survival of Purkinje cells. Injection of anti-mGluR1 IgG into the subarachnoid space of normal mice resulted in a reversible ataxia.[13,20] Moreover, mutations in the mGluR1 gene were found to induce rare forms of ataxia (i.e. autosomal recessive spinocerebellar ataxia type 13 [SCAR13][21] and autosomal dominant spinocerebellar ataxia type 44 [SCA44][22]). Based on these findings, anti-mGluR1 antibodies are considered directly pathogenic. However, the pathogenetic mechanism of anti-mGluR1 antibody formation is not fully understood. In seven cases, encephalitis has been suggested to be of paraneoplastic origin, being mainly associated with lymphomas.[13,16,17]

Independent of the association with a malignancy, most patients benefit from immunotherapy.[13–18] Until now, there are only few data on the long-term clinical course and treatment options for patients with anti-mGluR1 antibody-associated encephalitis. Here we present the clinical course of a man with anti-mGluR1 autoimmune encephalitis and provide an overview of the cases published so far.

Case report

A 45-year-old, otherwise healthy man with no relevant medical history presented with a 4-week history of progressive dysarthria. Neurological examination was unremarkable except for a moderate dysarthria. Brain MRI showed discrete fluid-attenuated inversion recovery (FLAIR) hyperintensity in the medial thalamus and pulvinar predominantly on the left (Figure 1). T2-weighted images disclosed the same signal changes. No contrast enhancement or diffusion restriction could be observed. MRI volumetry revealed that the cerebellar volume (white substance, cortex and total) was in the lower range of the age-related reference values. Electroencephalography (EEG) demonstrated abnormal intermittent general delta and theta frequency activity with frontal predominance (Figure 2).

CSF analysis revealed a mild lymphocytic pleocytosis (7 leucocytes/µl) with normal glucose and protein levels and no oligoclonal IgG bands (oligoclonal band pattern type I). Blood and CSF tests for viral or bacterial infections were negative, except for a resolved hepatitis B infection (hepatitis B surface antigen (HBsAg) negative, antibody to hepatitis B surface antigen (anti-HBs) > 1000 IU/L, andibodiy to hepatitis B core antigen (anti-HBc) positive, hepatitis B virus (HBV)-DNA negative). Autoantibodies possibly associated with an autoimmune encephalitis, including antibodies against N-methyl-D-aspartate receptor (NMDAR), leucine-rich glioma-inactivated 1 (LGI1), contactin-associated protein-like 2 (CASPR2), glycine receptor (GlyR), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor 2 (AMPAR2), IgLON family member 5 (IgLON5), γ-aminobutyric acid-B receptor (GABABR), metabotropic glutamate receptor 5

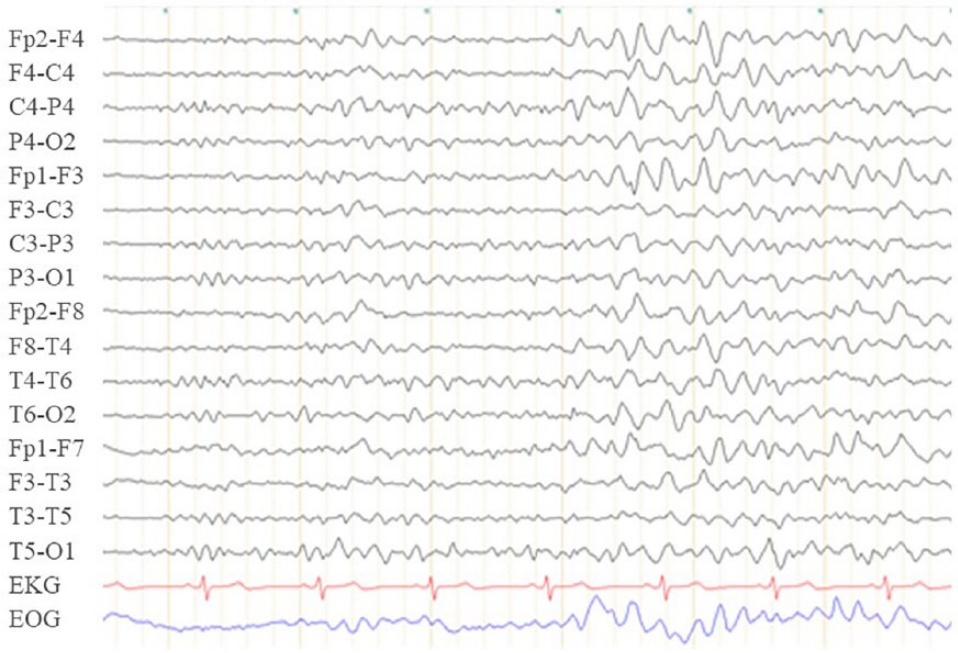

Figure 2. Electroencephalography (EEG) with intermittent general delta frequency activity with frontal predominance.

(mGluR5), dipeptidyl-peptidase-like protein 6 (DPPX), Hu, Ri, Yo, collapsin response mediator protein 5 (CV2/CRMP5), amphiphysin, Ma2, glutamic acid decarboxylase (GAD), Recoverin, Sry-like high mobility group box protein 1 (Sox1), Zic family member 4 (Zic4), delta/notch-like epidermal growth factor-related receptor (DNER) and unspecified neuropil antibodies were analysed in serum and CSF. Both samples showed immunohistochemically high reactivity with the neuropil of mouse brain, but no specific antibodies were detected by indirect immunofluorescence assays. The additional laboratory assessment was positive for antinuclear antibodies (ANAs) at 1:1600 (nucleolar pattern) without further clinical or laboratory evidence for rheumatic diseases. A whole-body positron emission tomography (PET) revealed no pathological finding.

Based on imaging and laboratory findings, an autoimmune encephalitis was assumed and the patient was treated with i.v. methylprednisolone (1.0 g/day for 3 consecutive days), followed by an oral prednisolone therapy (started at a dose of 70 mg/day) resulting in a marked improvement of dysarthria, confirmed by logopaedic assessment. CSF analysis 1 month later showed a normal cell count; neuropil antibodies were not detectable in blood and CSF. The ANA titre decreased to 1:800. Prednisolone was gradually tapered and discontinued after 4 months. About 3 months later, the patient presented with increasing dysarthria and a new occurrence of gait ataxia. The MRI again showed FLAIR hyperintensity in the medial thalamus and pulvinar predominantly on the left (Figure 1). The CSF cell count showed a slight increase (5 leucocytes/µl). Neuropil antibodies in CSF and blood were again positive. Further laboratory tests detected high-titre anti-mGluR1 IgG in CSF (1:32) and serum (1:1000), establishing the diagnosis of an anti-mGluR1-associated encephalitis. Anti-mGluR1 antibodies were also detected in the preserved CSF and serum samples of the first disease episode (CSF 1:32, serum 1:1000) and belonged to the IgG1, IgG3 and IgG4 subclass. The patient received a further course of i.v. methylprednisolone at a dose of 1.0 g/day for 3 consecutive days, which resulted in clinical improvement. From May 2017 the patient was treated with six courses of IVIG (loading dose with 2 g/kg over 5 consecutive days, maintenance dose of 1 g/kg monthly) with concomitant low-dose prednisolone. Anti-mGluR1 IgG titres in CSF (1:3.2) and serum (1:100) decreased and the patient showed a stable course with only mild dysarthria and mild gait ataxia over 6 months. In the

further course, anti-mGluR1 IgG in serum slowly increased (1:1000) followed by a slight worsening of dysarthria. We therefore initiated a B cell-depleting therapy with rituximab (two 1000 mg doses 2 weeks apart, then 1000 mg every 6 months) resulting in a stable clinical course. At 6 months after starting rituximab MRI demonstrated a regression of the hyperintense lesion in the medial thalamus and pulvinar and EEG still showed intermittent bifrontal theta and delta frequency activity. Neuropsychological evaluation revealed no relevant impairment and there was no dysgeusia. The last follow up 2 years after the first presentation and 10 months after starting rituximab showed a gradual improvement of dysarthria with persistent mild gait ataxia. The serum anti-mGluR1 antibodies decreased to 1:320. After two cycles of rituximab, B cells were effectively depleted (CD19+ - cells 0.02% of total lymphocytes) and HBV-DNA remained negative without prophylactic HBV treatment. A whole-body PET again was negative regarding a malignancy. MRI volumetry revealed no significant change in cerebellar volume between 2016 and 2018.

Clinical course, laboratory findings and treatment are shown in Figure 3.

The patient gave written informed consent for publication of this case report.

Review of reported cases

A systematic literature research *via* PubMed was conducted to identify previously reported cases of anti-mGluR1 antibody-associated encephalitis, using the following key terms: ('metabotropic glutamate receptor type 1' OR 'mGluR1') AND ('autoantibodies' OR 'autoantibody' OR 'autoimmunity' OR 'antibody').

A total of 18 cases published up to 30 September 2018 were identified.[13–19] The mean age was 57.12 years (standard deviation 15.57 years, range 19–81 years); 10 were women. All patients developed cerebellar ataxia (n = 18/18), further symptoms included dysarthria (n = 9/18),[13–18] cognitive impairment (n = 5/18),[13,16,17] ocular symptoms (n = 7/18),[14,15,17,18,20] head titubation (n = 3/18)[13,14,19], dysgeusia (n = 4/18)[17] and psychiatric symptoms (n = 2/18),[17,19] related to the location of mGluR1 in the olfactory bulb and limbic system.[7–9] Five of the published cases had CSF pleocytosis (range 5–190 cells/µl)[13–15,17,18] and

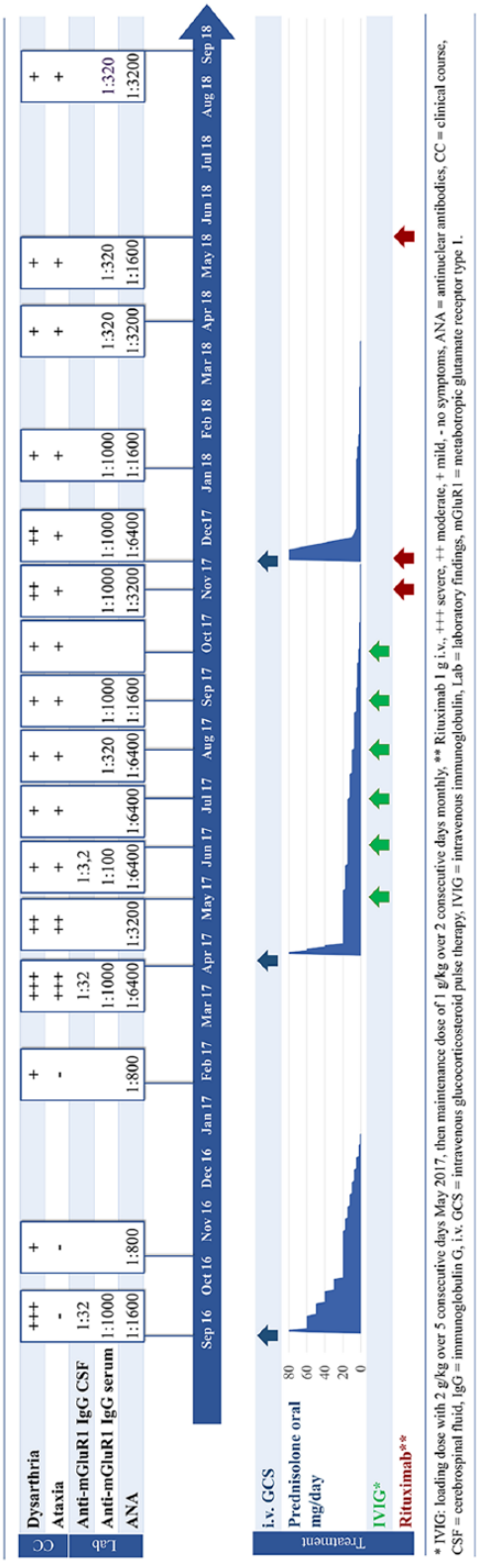

Figure 3. Clinical course, laboratory results and treatment. ANA, antinuclear antibodies; CSF, cerebrospinal fluid; IgG, immunoglobulin G; GCS, glucocorticoid pulse therapy; IVIG, intravenous immunoglobulin; mGluR1, metabotropic glutamate receptor type 1.

Table 1. Review of reported cases of anti-mGluR1 antibody-associated encephalitis.

No.	Author	Sex	Age (years)	Symptoms				Comorbidity	CSF	Anti-mGluR1 IgG serum	Anti-mGluR1 IgG CSF	cMRI	Treatment (time to treatment in months)	Follow up (duration in months)		
				Ataxia	Dysarthria	Cognitive impairment	Other symptoms							Clinical improvement	Anti-mGluR1 IgG serum	Anti-mGluR1 IgG CSF
1	Sillevis Smitt *et al.*[13]	F	19	+				Hodgkin's lymphoma (in remission)	Cells 28/µl, protein 0.28 g/L, OCBs negative	1:3200*	1:512*	Normal	Plasma exchanges, oral prednisone, IVIG (UNK)	↑ (7)	1:200 (1) – (7)	1:64 (1)
2	Sillevis Smitt *et al.*[13]	F	49	+	+	+	Impaired adaptation of saccadic eye movements[16], titubation of the head and trunk	Hodgkin's lymphoma (in remission), polycystic renal disease	UNK	1:3200*	+*	Normal (initial and after 6 months)	14 plasma exchanges (12)	↔ (UNK)	1:400 (UNK)	1:256 (UNK)
3	Marignier *et al.*[14]	F	50	+	+		Oscillopsia, vertical nystagmus, head titubation, headache	–	Cells 190/µl, protein 0.72 g/L, OCBs negative	1:20 000*	1:500*	Hyperintensity in the whole cerebellum on FLAIR and diffusion sequences	IVIG, oral prednisone, mycophenolate mofetil (1)	↑ (40)	1:500 (40)	UNK
4	Lancaster *et al.*[15]	M	69	+	+		Nystagmus, difficulty in fixation of gaze	–	Cells 8/µl, normal protein level	+*	+*	Initial: signs of small vessel ischaemic disease; 1 year later: cerebellar atrophy	i.v. GCS (6)	→ (UNK)	UNK	UNK
5	Iorio *et al.*[16]	M	65	+	+	+	Gaze nystagmus	Prostate adenocarcinoma, mycosis fungoides	Normal cell count, protein and glucose level	+*	+*	Mild cerebellar atrophy	IVIG, oral prednisone (UNK)	↑ (9)	UNK	UNK
6	Lopez-Chiriboga *et al.*[17]	M	64	+	+		Diplopia, nystagmus	–	Normal cell count, protein 0.43 g/L, OCBs negative	1:960*	UNK	Normal	Steroid, rituximab (UNK)	↑ Relapse after discontinuation of rituximab (17)	UNK	UNK

(Continued)

Table 1. (Continued)

No.	Author	Sex	Age (years)	Symptoms				Comorbidity	CSF	Anti-mGluR1 IgG serum	Anti-mGluR1 IgG CSF	cMRI	Treatment (time to treatment in months)	Follow up (duration in months)		
				Ataxia	Dysarthria	Cognitive impairment	Other symptoms							Clinical improvement	Anti-mGluR1 IgG serum	Anti-mGluR1 IgG CSF
7	Lopez-Chiriboga *et al.*[17]	M	54	+				–	UNK	1:1920*	1:256*	UNK	Steroid, IVIG (UNK)	→ (9)	UNK	UNK
8	Lopez-Chiriboga *et al.*[17]	M	81	+	+	+		–	Normal cell count and protein level, OCBs negative	1:1920*	1:64*	Mild global atrophy, T2 hyperintensity in the central superior cerebellum	IVIG (6)	↑ (24)	UNK	UNK
9	Lopez-Chiriboga *et al.*[17]	M	77	+				–	Normal cell count, protein 0. 85 g/L, OCBs negative	1:61440*	UNK	Cerebral atrophy	Steroid, IVIG (8)	→ (27)	UNK	UNK
10	Lopez-Chiriboga *et al.*[17]	M	51	+		+	Paranoia, auditory hallucination	Testicular seminoma	Cells 29/μl, normal protein level	1:7680*	UNK	Normal	Steroid, IVIG, plasma exchange (1)	↑ (11)	UNK	UNK
11	Lopez-Chiriboga *et al.*[17]	F	60	+	+	+		Sjögren's syndrome	Normal cell count and protein level, OCBs negative	1:3840*	UNK	Normal	Prednisone (2)	↑ (168)	UNK	UNK
12	Lopez-Chiriboga *et al.*[17]	F	58	+		+	Diplopia, vertigo	Herpes zoster	UNK	1:480*	UNK	Not done, cranial CT normal	None	↑ (6)	UNK	UNK
13	Lopez-Chiriboga *et al.*[17]	M	67	+				Cutaneous T-cell lymphoma	UNK	1:1920*	UNK	UNK	Chemotherapy for lymphoma (UNK)	→ (4)	UNK	UNK
14	Lopez-Chiriboga *et al.*[17]	F	67	+		+	Bilateral hand paraesthesias, vertigo	–	UNK	1:960*	UNK	Mild cerebral and cerebellar atrophy	None	↔ (60)	UNK	UNK

Table 1. (Continued)

No.	Author	Sex	Age (years)	Symptoms				Comorbidity	CSF	Anti-mGluR1 IgG serum	Anti-mGluR1 IgG CSF	cMRI	Treatment (time to treatment in months)	Follow up (duration in months)		
				Ataxia	Dysarthria	Cognitive impairment	Other symptoms							Clinical improvement	Anti-mGluR1 IgG serum	Anti-mGluR1 IgG CSF
15	Lopez-Chiriboga *et al.*[17]	F	33	+	+	+		ALL, RRMS	Elevated OCBs	1:1000**	–	Multiple brain and spinal cord T2 lesions, enhancing in brain	Steroid (3)	↑ (6)	UNK	UNK
16	Lopez-Chiriboga *et al.*[17]	F	77	+		+	Spastic right foot paresis	Mantel cell NHL, PPMS	Elevated OCBs	1:3200**	UNK	Multiple brain and spinal cord T2 lesions, nonenhancing	Rituximab, bendamustine (36)	↔ (4)	UNK	UNK
17	Yoshikura *et al.*[18]	F	61	+	+		Abnormal smooth-pursuit eye movements, dysphagia	Elevated serum ANA	Cells 5/µl, protein 0.29 g/L, glucose 3.86mmol/L	1:3200*	+*	Initial normal; 57 months after onset cerebellar atrophy	i.v. GCS, IVIG, plasma exchanges, rituximab, oral prednisolone, tacrolimus, azathioprine (2)	↑ (65)	1:800 (7) 1:100 (65)	UNK
18	Pedroso *et al.*[19]	F	39	+			Apathy, catatonia, head titubation	–	UNK	1:12*	1:512*	Normal	UNK	UNK	UNK	UNK

*Tissue-based and cell-based immunofluorescence assay positive; **cell-based immunofluorescence assay positive and tissue-based immunofluorescence assay weakly positive. + positive, - negative, ↑ clinical improvement, → stabilized course, ↔ no therapeutic effect. ALL, acute lymphocytic leukaemia; ANA, antinuclear antibodies; cMRI, cranial magnetic resonance imaging; CSF, cerebrospinal fluid; CT, computed tomography; F, female; FLAIR, fluid-attenuated inversion recovery; GCS, glucocorticoid pulse therapy; IgG, immunoglobulin G; IVIG, intravenous immunoglobulin; M, male; mGluR1, metabotropic glutamate receptor type 1; NHL, Non-Hodgkin lymphoma; OCB, oligoclonal IgG band; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis, UNK, unknown.

oligoclonal IgG bands were detected in two patients diagnosed with multiple sclerosis.[17] In six cases MRI showed a cerebellar T2-hyperintensity or cerebellar atrophy,[14–18] whereas six patients had a normal MRI.[13,17,19]

Table 1 summarizes the clinical presentation, diagnostic results and treatment of the cases published so far.

Discussion

Due to the variable clinical manifestation and diagnostic findings, the diagnosis of anti-mGluR1 antibody-associated encephalitis is challenging. The case reported is the first patient diagnosed with anti-mGluR1 antibody-associated encephalitis who initially suffered from isolated progressive dysarthria and developed subacute ataxia months later. The mild CSF pleocytosis was consistent with autoimmune encephalitis after excluding an infectious disorder. MRI abnormalities in our case differed from cases reported so far, since they were not located in the cerebellum, but in the thalamus and pulvinar. This finding may reflect the different expression of mGluR1 in the human brain[6–9] and indicates that anti-mGluR1 antibodies can not only cause cerebellitis, but can also affect distinct brain areas. A recent retrospective MRI study in patients with basal ganglia haemorrhage concluded that lesions in the left pulvinar nucleus can lead to dysarthria.[23] Since the FLAIR hyperintensity of the case reported was predominantly detected in this region, dysarthria as initial presentation can be explained. Whether ataxia, observed in our case, has also been caused by a thalamic instead of cerebellar involvement cannot be determined unequivocally, since thalamic lesions can also cause cerebellar-like ataxia.[24]

Another finding was the nonspecific EEG abnormality with intermittent generalized delta and theta frequency activity with frontal predominance that was observed throughout the whole follow-up period without clinical correlation. Nonspecific EEG abnormalities have been described in other autoimmune encephalitis entities and can be the only diagnostic finding when MRI and CSF are normal.[25] Hence, EEG is an important diagnostic tool, but does not seem to be suitable for treatment monitoring.

The pathogenesis of the autoimmune condition in the current case remains obscure. Previously different pathophysiological mechanisms of anti-mGluR1 antibody-associated encephalitis have been discussed. Several cases (n = 7/18) have been reported to be paraneoplastic: 5 out of the 18 patients reported in the literature had a lymphoma,[13,16,17] 1 patient had an acute lymphatic leukaemia,[17] 1 patient suffered from a prostate adenocarcinoma[16] and 1 patient had a history of testicular seminoma.[17] The frequent association of especially lymphomas and anti-mGluR1 antibody-associated encephalitis suggests a paraneoplastic context. However, the long interval between lymphoma manifestation and cerebellar syndrome onset in the first two cases (lymphoma in remission for 2 years and 9 years)[13] as well as the lack of mGluR1 expression in tumour lymph nodes of the index patient[13] have raised doubts concerning the paraneoplastic link between lymphoma and anti-mGluR1 antibodies. However, in a patient with prostate adenocarcinoma and ataxia, anti-mGluR1 IgGs have been shown to bind to abundant mGluR1 expressed by epithelial cells of the adenocarcinoma.[16] In addition aberrant expression of mGluR1 in other tumours such as breast cancer,[26,27] melanoma[28] and glioma[29] has been reported. Therefore, subacute cerebellar ataxia of unknown origin always requires an extended tumour screening.

Parainfectious autoimmunity is another potential pathophysiological mechanism. Lopez-Chiriboga and colleagues described a patient with herpes zoster 1 month prior to clinical manifestation of anti-mGluR1 antibody-associated cerebellitis.[17] Similar phenomena with a concomitant or preceding herpes simplex or varicella zoster infection have been observed in patients with NMDAR encephalitis.[30–33]

Beside the association with various tumours and a parainfectious aetiology, five patients with a comorbid autoimmune disease were reported: coexistent Sjögren's syndrome in one, hypothyroidism in one, pernicious anaemia in one and multiple sclerosis in two patients.[17] Remarkably, laboratory tests of the case reported here revealed an elevated ANA titre with nucleolar pattern without clinical signs of rheumatic or other autoimmune disease. Similar findings have been obtained by Yoshikura and collegues.[18] Detection of ANAs without related symptoms have been described in association with other forms of autoimmune encephalitis[34,35] possibly indicating a disposition for autoimmunity in those patients.

Regardless of the aetiology of anti-mGluR1 antibody-associated encephalitis, early treatment seems to be important. Yoshikura and colleagues assumed that early treatment is crucial, because chronic exposure of the Purkinje cells to anti-mGluR1 antibodies can induce cell degeneration of Purkinje cells and thus results in a progressive irreversible cerebellar atrophy.[18] This is supported by the observation that postmortem analysis of the cerebellum of a patient with anti-mGluR1 antibodies revealed abnormal density and morphology of the Purkinje cells[20] and that some patients with an initially normal brain MRI develop cerebellar atrophy in clinical course.[15,18] Early and effective immunotherapy is therefore essential to prevent irreversible damage to the Purkinje cells. This assumption is supported by the fact that patients showing no clinical improvement under immunotherapy had a long interval between disease onset and treatment (36 months and 12 months),[13,17] whereas in patients improving or stabilizing under immunotherapy, treatment has been initiated within 1–8 months after symptom onset.[13–18] In five cases reported in the literature, the interval to treatment has not been documented.

Various therapeutics have been effective in the previously reported cases. At disease onset glucocorticosteroids, IVIG and plasma exchange have been used in the majority of patients.[13–18] In our case glucocorticosteroids and IVIG initially resulted in clinical improvement, but during IVIG therapy dysarthria worsened, so treatment was switched to rituximab, which has been applied in three previous cases of anti-mGluR1 antibody-associated encephalitis so far. One patient clinically improved with rituximab and relapsed after treatment discontinuation.[17] Another patient[17] starting therapy 36 months after the onset of ataxia showed no benefit and the third patient[18] received only a single course of rituximab. Our patient has shown a stable clinical course since starting B-cell depletion, but due to the short treatment duration (approximately 10 months) and the limited data from previous cases, further studies are necessary to demonstrate whether a B cell-depleting therapy is an effective treatment in general. As an alternative to rituximab, cyclophosphamide is an established second-line therapy for autoimmune encephalitis, but has an unfavourable side-effect profile.[4] Recent studies moreover identified the plasma cell-depleting proteasome inhibitor bortezomib[36,37] and the humanized anti-interleukin-6-receptor antibody tocilicumab[38,39] as possible escalation therapy for inadequate treatment response to second-line therapies. However, due to the limited data available, further studies are required.

In our case, anti-mGluR1 IgG subclass differentiation revealed the subclasses IgG1, IgG3 and IgG4. In no other case published so far have mGluR1 antibody IgG subclasses been described. Previous studies identified predominantly IgG1 in anti-NMDAR[40] and anti-mGluR5[41] encephalitis, while autoantibodies against CASPR2,[42] LGI1[43,44] and IgLon5[45] were mainly of the IgG4 subclass. However, since the pathophysiology of the different IgG subclasses in autoimmune encephalitis is largely not understood, further studies are necessary, and also to explore possible therapeutic consequences.

The case reported here is the second long-term follow up of a patient with anti-mGluR1 antibody-associated encephalitis. A remarkable finding during follow up was the correlation of the serum anti-mGluR1 antibody titre and the independently (by neurologists and speech therapists) assessed dysarthria severity (Figure 3). Based on that and the hitherto published cases showing a decrease in anti-mGluR1 IgG titre under treatment,[13,14,18] serum anti-mGluR1 IgG titre may be a useful marker for monitoring immunotherapy, as also suggested by Yoshikura and colleagues.[18] Whether the CSF antibody titre also correlates with the clinical course, as shown in anti-NMDA encephalitis,[46,47] has to be addressed by further studies.

In conclusion, based on the case reported here and the review of the literature, diagnosing anti-mGluR1 antibody-associated encephalitis is challenging. To prevent permanent sequelae, early diagnosis and effective treatment are crucial.

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Conflict of interest statement

AB has received personal compensation for activities with Roche.

ORCID iD
Monika Christ https://orcid.org/0000-0002-8071-1501

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