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Progressive Encephalomyelitis With Rigidity and Myoclonus With Glycine Receptor Antibodies

Clinical Features and Outcomes

Mar Guasp,[1,2,*] Albert Saiz,[1,2,*] Marina Ruiz-Vives,[1] Miriam Almendrote,[3] Jordi Bruna,[4] Jordi González-Menacho,[5] Juntaro Kaneko,[6] Lorena Martín-Aguilar,[7,8] Francisco Antonio Martínez-García,[9] Kazuyuki Noda,[10] Angel Ruiz Molina,[11] Sara Sequeiros,[12] Mateus Mistieri Simabukuro,[13] Megumi Takenaka,[14] Martín Zurdo,[15] Josep O. Dalmau,[1,2,16,17,†] Takahiro Iizuka,[6,†] and Francesc Graus[2,†]

Correspondence
Dr. Guasp
guasp@clinic.cat or
Dr. Graus
fgraus@recerca.clinic.cat

Neurol Neuroimmunol Neuroinflamm 2025;12:e200473. doi:10.1212/NXI.0000000000200473

Abstract

Background and Objectives

The aim of this study was to describe the clinical features and long-term outcome of patients with glycine receptor (GlyR) antibody–mediated progressive encephalomyelitis with rigidity and myoclonus (PERM), a disease commonly included under the term of stiff-person spectrum disorders (SPSDs).

Methods

We conducted a retrospective analysis of patients with PERM and GlyR antibodies diagnosed in our laboratory and a systematic literature review (following Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] 2020 reporting guideline) of previously reported patients with sufficient clinical information and ≥12 months of follow-up. Neurologic disability was measured with the modified Rankin Scale (mRS). Relapses were defined as any event occurring >6 months after the first episode that required immunotherapy.

Results

Forty-one patients were identified, 22 from our database and 19 from the literature. The median age was 58 years (IQR: 43–66 years), and 36 (88%) were male and 5 female. The median time from symptom onset to admission was 2 weeks (IQR: 1–4 weeks). Predominant presentations included brainstem symptoms, mainly dysphagia and trismus, in 23 patients (56%); muscle stiffness and myoclonus in 9 (22%); dysesthesias or pruritus in 7 (17%); and cacosmia with dysgeusia in 2 (5%). Five patients (12%) never developed muscle stiffness. The median (range) mRS score at nadir was 5 (3–5). All patients received immunotherapy. Eleven patients died, 8 from complications of PERM. There were 12 relapses in 10 (28%) of 36 patients who lived >6 months. All relapses responded to immunotherapy. The functional status at the last visit, median time 24 months (IQR: 18–72 months), was good (mRS score <3) in 23 (70%) of the 33 patients who did not die from PERM. Age (HR: 1.06; 95% CI 1.01–1.11; p = 0.019) and admission to the intensive care unit (HR: 5.26; 95% CI 1.41–19.57, p = 0.013) were independent predictors of bad outcome (mRS score ≥3).

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Supplementary Material

*These authors contributed equally to this work as co-first authors.

†These authors contributed equally to this work as co-senior authors.

[1]Service of Neurology, Hospital Clinic, University of Barcelona, Spain; [2]Neuroimmunology Program, Institut d'Investigació Biomèdica August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [3]Department of Neuroscience, Hospital Universitari Germans Trias i Pujol, Universitat Autònoma de Barcelona, Spain; [4]Neuro-Oncology Unit, Hospital Universitari de Bellvitge-ICO l'Hospitalet, IDIBELL (Oncobell Program), Barcelona, Spain; [5]Neurology Unit, Hospital Universitari de Sant Joan, Institut d'Investigació Sanitària Pere Virgili, Universitat Rovira i Virgili, Reus, Spain; [6]Department of Neurology, Kitasato University School of Medicine, Sagamihara, Japan; [7]Department of Neurology, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Spain; [8]Neurological Diseases, Institut de Recerca Sant Pau, Barcelona, Spain; [9]Department of Neurology, Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain; [10]Department of Neurology, Juntendo University Shizuoka Hospital, Izunokuni, Japan; [11]Service of Neurology, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain; [12]Service of Neurology, Hospital Alvaro Cunqueiro, Vigo, Spain; [13]Division of Neurology, Hospital das Clinicas, Faculdade de Medicina, Universidade de Sao Paulo, SP, Brazil; [14]Department of Neurology, Chugoku Rosai Hospital, Kure, Hiroshima, Japan; [15]Department of Neurology, Hospital Virgen del Puerto, Plasencia, Spain; [16]Department of Neurology, University of Pennsylvania, Philadelphia; and [17]Caixa Research Institute (CRI), Barcelona, Spain.

The Article Processing Charge was funded by the authors.

Glossary

CTX = cyclophosphamide; **GAD** = glutamic acid decarboxylase; **GlyR** = glycine receptor; **ICU** = intensive care unit; **ISCIII** = Instituto de Salud Carlos III; **mRS** = modified Rankin Scale; **PERM** = progressive encephalomyelitis with rigidity and myoclonus; **RTX** = rituximab; **SPS** = stiff-person syndrome; **SPSD** = stiff-person spectrum disorder.

Discussion

GlyR antibody–mediated PERM is a rapidly progressive and severe disease that predominantly affects men and frequently presents with brainstem involvement. Its distinct demographic and clinical features suggest that it should be considered separately from SPSDs, which typically follows a chronic course and is more commonly associated with glutamic acid decarboxylase antibodies.

Introduction

The term "progressive encephalomyelitis with rigidity and myoclonus (PERM)" was introduced by Prof. Meinck[1] to describe a syndrome previously referred to as "progressive encephalomyelitis with rigidity"[2] or "subacute myoclonic spinal neuronitis,"[3] characterized by subacute onset of muscle stiffness, rigidity, and spasms resembling stiff-person syndrome (SPS), accompanied by brainstem signs such as diplopia, gaze palsies, bulbar symptoms, stimulus-sensitive myoclonus, and autonomic features including hyperhidrosis.[4,5] PERM is regarded as a variant of SPS and included within the SPS spectrum disorders.[6] This idea was initially supported by the detection of glutamic acid decarboxylase (GAD) antibodies, the hallmark of SPS, in an early PERM series, where 22 (76%) of 29 patients tested positive.[5] Moreover, patients with longstanding, otherwise typical, SPS may later develop additional features suggestive of PERM.[7,8] However, since the 2008 description of a patient with PERM who had glycine receptor (GlyR) antibodies,[9] these antibodies have become the most commonly reported in PERM and, unlike GAD antibodies, their pathogenic role is supported by passive antibody transfer models.[10,11] These findings suggest that GlyR antibody–mediated PERM represents a distinct disorder and should be analyzed separately from the SPS spectrum, which is more commonly associated with GAD antibodies. Because serum low-titer GlyR antibodies can be detected in multiple disorders,[12] PERM cases are often grouped with other syndromes in GlyR antibody series, with limited clinical information typically summarized in tables, making it difficult to capture key clinical details such as presenting symptoms and long-term outcomes.[10,13-15]

In this study, we describe the detailed clinical features and outcome of patients with PERM and GlyR antibodies, either diagnosed in our laboratory or previously reported with sufficient clinical information and follow-up.

Methods

Patients

We retrospectively identified patients with PERM whose serum or CSF samples were sent to our laboratory and were found positive for GlyR antibodies using a previously reported in-house live cell-based assay of HEK293 cells expressing the GlyR α1 subunit.[16] Patients with concomitant GAD or other neuronal antibodies against cell-surface antigens were excluded. Clinical and demographic features, paraclinical data including CSF (cell count, protein levels, and oligoclonal bands), EMG, and brain and spinal cord MRI findings and treatments received were obtained from medical records and information provided by the referring physicians through a structured questionnaire. In 2025, referring physicians were contacted again to obtain information on potential relapses, maintenance treatments, and neurologic status at the last visit. Patients were included in the study only if there was adequate clinical information compatible with the definition of PERM (muscle rigidity, spasms, myoclonus, or brainstem dysfunction),[4,5] GlyR antibodies, and a follow-up of at least 12 months, except for those patients who died earlier, since onset of PERM. Exclusion criteria included the following: (1) limited clinical information or follow-up; (2) age younger than 15 years; (3) GlyR antibodies but diagnosis other than PERM; (4) atypical features, such as spontaneous improvement of symptoms; (5) concurrent neuronal antibodies; and (6) a chronic clinical course typical of SPS with overlapping symptoms, for example, diplopia, suggestive of PERM.

In addition, we performed a systematic literature review. Patients were identified through a comprehensive PubMed search (from January 2008 when GlyR antibodies were first described[9] to February 2025) using the terms "encephalomyelitis with rigidity and myoclonus" OR "glycine receptor antibody AND PERM" OR "glycine receptor antibody AND encephalomyelitis with rigidity and myoclonus." Only cases published in English that included detailed clinical information and follow-up ≥ 12 months were selected. We used the PRISMA 2020 reporting guideline to draft this article and the PRISMA 2020 reporting checklist when editing. The flow diagram outlining the patient selection process for this study is shown in Figure 1. Clinical records of patients identified in the laboratory database, along with articles from the literature search, were independently reviewed by 3 investigators (MG, AS, FG), with discrepancies resolved through consensus.

Following the indicated criteria, we initially excluded 76 of 105 articles screened from the literature (listed in eAppendix 1) and 22 (50%) of 44 patients (eTable 1) from our database (Figure 1). Of the cases initially considered to have PERM and GlyR antibodies, we finally excluded 11 patients reported in 10 articles (eTable 2) and 3 patients diagnosed in our laboratory (eTable 3).

Neurologic disability was measured with the modified Rankin Scale (mRS).[17] A patient was considered improved if there was a decrease of at least 1 point in the mRS after treatment. For previously reported patients, the mRS score was calculated based on clinical descriptions. Relapses were defined as any event occurring >6 months after the first episode that led to symptom worsening or the development of new symptoms, requiring escalation of immunotherapy. Mild worsening of preexisting symptoms, sometimes in association with an intercurrent infection, was not considered a disease relapse.

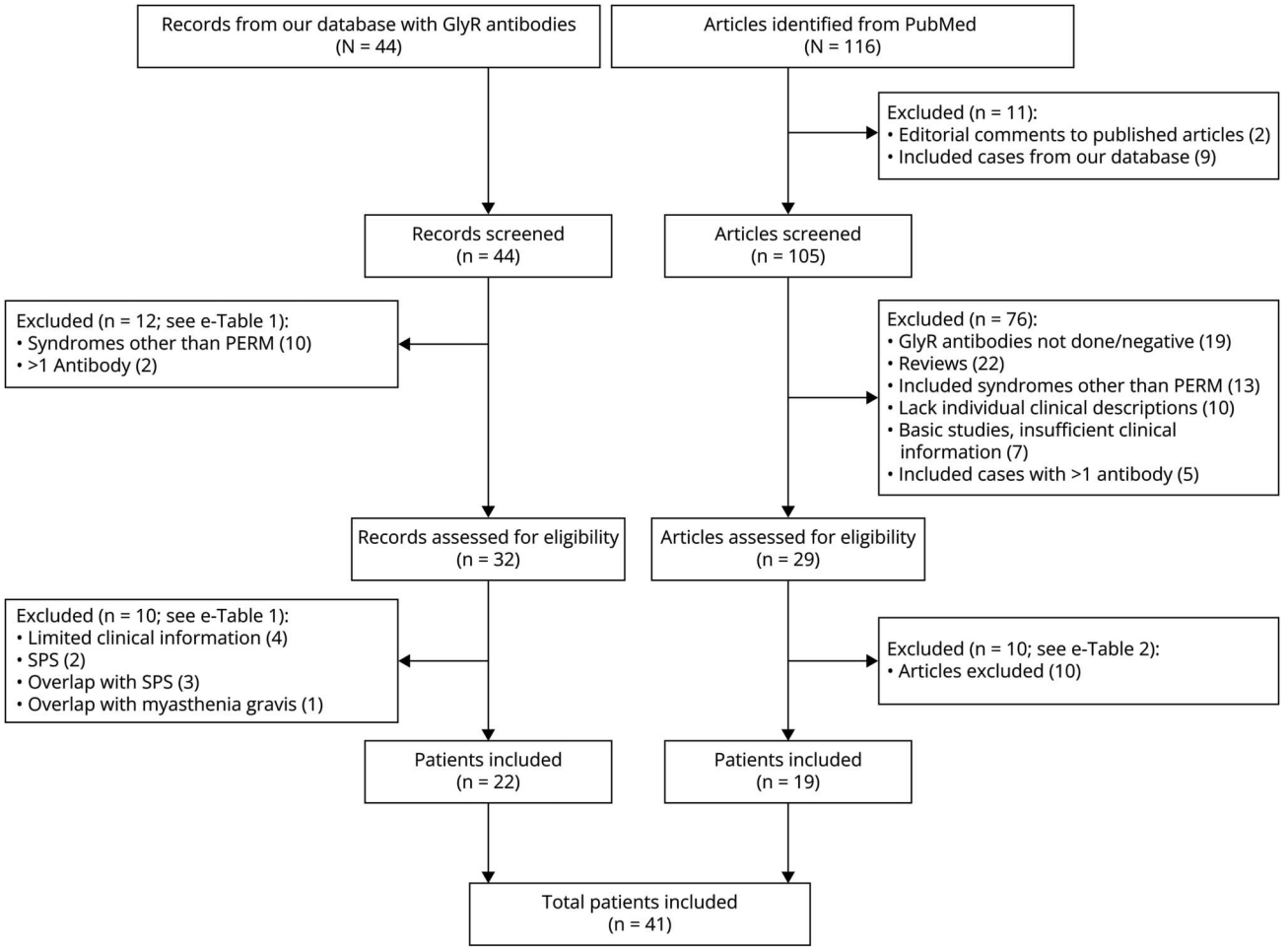
Statistical Analysis

All data are described as median and interquartile range (IQR; 25th, 75th percentiles) or absolute frequency and percentage for quantitative and qualitative variables, respectively. Because Gaussian distribution was not confirmed by Kolmogorov-Smirnov and Shapiro-Wilk normality tests, data were analyzed using nonparametric tests. To identify variables that potentially predicted a poor outcome (defined as mRS score ≥3 at last follow-up for each patient), we first conducted univariate Cox proportional hazard analyses. Variables that showed a statistically significant effect on the outcome in univariate analyses were subsequently included in a multivariate Cox regression model using a forward stepwise selection approach based on the Wald method. Variables entered the model at a significance level of $p < 0.05$ and were removed if $p \geq 0.05$. The number of variables that could enter the multivariate model was limited using the $p < m/10$ rule to prevent overfitting of the model. Hazard ratios with corresponding 95% CIs were calculated. All statistical tests were two-tailed, and a p value <0.05 was considered statistically significant. Analyses were performed using IBM SPSS Statistics (version 26).

Samples and Ethics Statement

Patients' serum and CSF samples are archived in the collection of biological samples named "Neuroinmunología" registered in the Biobank of Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS). Written informed consent was obtained

Figure 1 Flowchart of Patients Included in the Study



from all patients for the storage and use of their samples for research purposes. The study was approved by the Ethics Committee of the Hospital Clinic of Barcelona, Spain (HCB/2018/0192).

Data Availability

Anonymized data are available by reasonable request from qualified investigators.

Results

We identified 41 patients with PERM, GlyR antibodies, adequate clinical information, and follow-up of at least 12 months; 22 were from our database and 19 from the literature (Figure 1).

The median age of the 41 patients included was 58 years (IQR: 43–66 years); 36 (88%) were male and 5 female. In 10 patients (24%), the disorder was preceded by an infectious process: 4 with upper respiratory tract infections; 2 with varicella zoster; and 1 each with brucellosis, COVID-19, gastroenteritis, and fever with myalgia. Nine patients (22%) had systemic tumors: thymoma (2); Hodgkin lymphoma (2); and lung (2), breast (1), kidney (1), and bladder cancer (1) (eTable 4). Autoimmune comorbidities were present in only 3 patients (7%): 1 patient had psoriasis, 1 rheumatoid arthritis, and another type 1 autoimmune polyendocrine syndrome. GlyR antibodies were present in the serum and CSF of all patients (CSF was not tested in 7 patients (17%), 6 reported from the literature and 1 of the 22 diagnosed in our laboratory).

Symptoms developed rapidly, with a median time from symptom onset to hospital admission of 2 weeks (IQR: 1–4 weeks). Analysis of the most prominent symptom presentations revealed several clinical profiles: First, brainstem involvement, mainly bulbar, was observed in 23 patients (56%) (Tables 1 and 2). In 10 of these 23 patients, the most prominent symptom presentation was dysphagia, and in another 6, trismus. Four patients developed rapidly progressive respiratory distress that required intubation on the day of admission. The remaining 3 patients presented with ptosis, diplopia, or facial palsy. Muscle stiffness, painful spasms, and/or myoclonus occurred a few days or, more rarely, weeks after the brainstem symptoms and were present at admission in 13 (57%) of the 23 patients. Second, myoclonus and/or muscle stiffness and painful spasms were the main presenting clinical features in 9 patients (22%). Six of the 9 patients showed additional symptoms: hallucinations, facial palsy, diplopia, dysautonomia, dysphagia, or paresthesias (Tables 1 and 2). Third, focal or diffuse dysesthesias occurred as presenting symptoms in 7 patients (17%) (Tables 1 and 2); 3 of these patients defined the symptoms as pruritus. The dysesthesias did not have a myeloradicular or peripheral nerve distribution, and they were associated with muscle spasms, diplopia, headache, insomnia, or dysgeusia in 5 patients. Fourth, dysgeusia and cacosmia were the presenting symptoms in 2 patients (5%) (Table 1). One of these patients reported a persistent unpleasant odor and noted that meals tested rotten. A few days later, he had auditory hallucinations and myoclonus in the right side of the face and arm. The other patient developed cacosmia and dysgeusia concurrently with diffuse pruritus, more intense in the left side, and stiffness with spasms in the left leg.

The clinical symptoms of all 41 patients at the time of hospital admission are summarized in Table 3. Twenty-five patients (61%) had developed the triad of stiffness, muscle spasms, and myoclonus, along with brainstem symptoms suggestive of PERM. Eleven additional patients (27%) developed the same clinical profile during their hospital stay. However, 5 patients (12%) never presented muscle stiffness. Twenty-one patients (51%) required admission to the intensive care unit (ICU). Brain and spinal cord MRI, CSF, and EMG findings are given in eTable 5. CSF pleocytosis (median lymphocytes/μL: 22; range: 6–98) occurred in 23 (62%) of 37 patients. Positive CSF oligoclonal bands were identified in 10 (37%) of 27 patients. Brain and spinal cord MRI findings were unremarkable in all assessed patients. EMG showed continuous motor unit firing of agonist and antagonist muscles at rest or electrophysiologic features of myoclonus in 15 (58%) of 26 patients. EMG was reported normal in 8 patients and with changes unrelated to SPS in the remaining 3 patients (although CSF pleocytosis was present in 8 of them).

All patients received immunotherapy that included combinations of intravenous methylprednisolone, immunoglobulins, or plasma exchange (Tables 1 and 2). Sixteen patients (39%) also received rituximab (RTX) or cyclophosphamide (CTX). By the time of hospital discharge, 31 (77%) of 40 patients had improved. One patient was not assessable because of a cardiac arrest and remained in postanoxic coma through the clinical course. The median mRS score at nadir was 5 (range: 3–5) and at discharge was 3 (range: 0–6). Improvement was observed in 14 (87.5%) of 16 patients who received RTX or CTX and in 19 (76%) of 25 who did not ($p = 0.45$).

By the last follow-up, 11 patients (27%) had died, 8 (20%) due to complications of PERM and 3 from complications of the underlying cancer or COVID-19 infection. Age was the only variable associated with death (HR: 1.09; 95% CI 1.02–1.16. $p = 0.006$). The median age of patients who died was 70 years (range: 60–80 years) compared with 54 years (range: 16–82 years) of those who were alive or who died from causes unrelated to PERM. Among the 36 patients who lived >6 months, 12 relapses were identified in 10 (28%) (Tables 1 and 2). The median time to relapses was 16 months (range: 7–67 months). Relapses occurred while patients were on maintenance immunotherapy (6 patients) or stopped the medication (2). Clinical features at relapse typically involved a recurrence or worsening of symptoms present during the

Table 1 Demographic and Clinical Data of 22 Patients With PERM and GlyR Antibodies Diagnosed in Our Laboratory

Patient Age/sex	Presenting symptoms	PERM triad[a]	Immunotherapy	mRS score before/ after treatment	Maintenance immunotherapy (mo)	Relapses (mo of follow-up)	Last mRS score (mo of follow-up)
1. 30–40/M	Pruritus in R face, neck, and shoulder; 7 days later, rigidity and painful spasms in R leg and bright visual scotomas	Yes, at admission	IVIG, IVMP, PLEX, RTX, CTX	5/4	RTX (36), tacrolimus (48)	Yes (67)	2 (79)
2. 40–50/M	Dysphagia, dysarthria, pruritus, insomnia, and later diplopia	Yes, at follow-up	IVIG, IVMP, PLEX, RTX	5/3	RTX (24), AZA (24)	No	2 (30)
3. 60–70/M	Dysphagia, diplopia, and dizziness; 1 wk later, trismus and central hypoventilation	No, never stiffness or myoclonus	IVMP, RTX	5/3	RTX (30), mycophenolate (30)	No	1[d] (36)
4. 80–90/M	Diffuse pruritus and painful muscle spasms in legs; later ptosis and dysarthria	Yes, at admission	Oral prednisone	4/4	IVIG (24)	No	2 (120)
5. 20–30/M	Dysphagia, abdominal discomfort, weight loss, constipation, pruritus, diplopia, and orthostatic hypotension	Yes, at follow-up	IVIG, IVMP, PLEX, RTX, prednisone	4/3	RTX (70)	Yes (59)	1 (77)
6. 50–60/M	Cacosmia, dysgeusia, and pruritus; later rigidity, muscle spasms in L leg, and diplopia	Yes, at admission	IVIG, IVMP, RTX	4/2	RTX (12)	No	0 (72)
7. 30–40/M	Cacosmia and dysgeusia; a few d later, auditory hallucinations, myoclonus in R face, arm, and diplopia	No, never stiffness	IVIG, oral prednisone	4/2	Prednisone (17)	No	0 (21)
8. 80–90/M	Diplopia x 3 wk, later painful muscle spasms and trismus	Yes, at follow-up	IVIG, IVMP, RTX	4/3	RTX (6)	No	0[d] (13)
9. 60/M[18]	Dysphagia for 5 d, later diplopia, painful muscle spasms, and stiffness	Yes, at admission	IVIG, IVMP	5/NA[c]	NA	NA	6 (36)
10. 40–50/M[18]	Generalized pruritus, anxiety, dysgeusia, hypersomnia; a few wks later, trismus, muscle rigidity, and painful spasms	Yes, at admission	IVIG, oral prednisone	4/3	No	No	3 (192)
11. 67/M[19]	Respiratory distress, myoclonus, dysphagia, and spasticity in legs	Yes, at admission	IVIG, IVMP, PLEX	5/4	AZA (30)	Yes (12)	5 (36)
12. 50–60/F	Myoclonus, diplopia, R facial palsy, and visual hallucinations for 1 month; later dysphagia and constipation	No, never stiffness	IVIG, IVMP	5/2	No	No	1 (105)
13. 30–40/M	Myoclonus, rigidity, hyperhidrosis, and urinary retention	Yes, at admission	IVMP	4/1	No	No	0 (23)
14. 60–70/M	Diplopia, trismus, L facial spasm, and rigidity in L leg	Yes, at admission	IVIG, IVMP	5/5	NA	NA	6 (6)
15. 60–70/M	Trismus (isolated x 5 mo), myoclonus, R leg stiffness, and dysautonomia	Yes, at admission	IVIG, IVMP, CTX	5/3	Cy (67), prednisolone (34)	Yes (14)	0 (99)
16. 70–80/M[20]	Dysarthria and dysphagia; 8 d later, vertical gaze palsy and leg rigidity	Yes, at admission	IVIG, IVMP	5/5	NA	NA	6 (2)
17. 50–60/M	Dysphagia and dysarthria; 18 d later, paroxysmal muscle spasms and hyperhidrosis	Yes, at admission	IVIG	5/3	Prednisolone (60), tacrolimus (60)	Yes (18, 52)	1 (64)
18. 50–60/M	Ptosis, hyperhidrosis, urinary retention, constipation, and depression	Yes, at admission	IVIG, IVMP, CTX	5/4	Prednisolone (87), AZA (87)	Yes (10, 39)	2 (93)
19. 63/M[21]	Dysphagia and painful lower limb muscle stiffness for 4 mo, followed by myoclonus	Yes, at admission	IVIG, IVMP	5/4	Prednisolone (7), AZA (7)	No[b]	4 (15)
20. 71/M[22]	Trismus and L facial stiffness; 16 d later and muscle rigidity and myoclonus in both legs	Yes, at admission	IVIG, IVMP	5/3	Prednisolone (6)	No	6 (8)

Continued

Table 1 Demographic and Clinical Data of 22 Patients With PERM and GlyR Antibodies Diagnosed in Our Laboratory *(continued)*

Patient Age/sex	Presenting symptoms	PERM triad[a]	Immunotherapy	mRS score before/ after treatment	Maintenance immunotherapy (mo)	Relapses (mo of follow-up)	Last mRS score (mo of follow-up)
21. 59/M[23]	Itching/dysesthesias in R ear, neck, and face and headache; two wk later, diplopia and decreased level of consciousness	Yes, at follow-up	IVIG, IVMP, PLEX, RTX, CTX	5/5	Cy (60), prednisolone (60)	No	5 (65)
22. 70–80/F	Dizziness and mild instability, followed by severe dysphagia and episodes of laryngeal stridor	Yes, at admission	IVIG, IVMP	5/2	RTX	No	1 (29)

Abbreviations: AZA = azathioprine; CTX = cyclophosphamide; CY = cyclosporine; IVIG = IV immunoglobulin; IVMP = IV methylprednisolone; PLEX = plasmapheresis; RTX = rituximab.
[a] Combination of brainstem symptoms, muscle stiffness, and myoclonus or muscle spasms.
[b] Suspected relapse but no clinical information available.
[c] Not applicable, patient in postanoxic coma after cardiac arrest.
[d] mRS score at the time the patient died of causes not related to PERM.

initial episode. The prognosis of the relapses was good, as all patients responded to treatment (Table 4). The median follow-up duration for the 33 patients who were alive or had not died of PERM complications was 24 months (IQR: 18–72 months). The mRS score at the last visit of these 33 patients was <3 in 23 (70%), but 10 (30%) remained with moderate (mRS score = 3; 4 patients) or severe (mRS score >3; 6 patients) deficits (Figure 2). Univariate analysis of outcome predictors, categorized as good (mRS score <3) vs poor (mRS score ≥3), is shown in eTable 6. In the multivariate analysis, patient's age (HR: 1.06; 95% CI 1.01–1.11; $p = 0.019$) and ICU admission (HR: 5.26; 95% CI 1.41–19.57, $p = 0.013$) were identified as risk factors of bad outcome.

Discussion

These findings provide robust evidence that PERM associated with GlyR antibodies is a distinct clinical entity, separate from other syndromes within the SPS spectrum disorder, which are primarily driven by GAD autoimmunity. The initial association between PERM and SPS was based on overlapping symptoms, primarily muscle stiffness and spasms, and the frequent detection of GAD antibodies.[4,5] Early PERM series, published before the discovery of GlyR antibodies, reported a predominance of women (59%) and a median age at onset of 46 years[5] By contrast, the median age at onset in this series, focused on PERM with GlyR antibodies, was older, 58 years, and 88% of patients were male. A similar male predominance, though not so high (67%), was also seen among 31 adult patients classified as PERM and included in a series of 45 patients with GlyR antibodies.[10] Another key difference with SPS and SPS variants is that patients with PERM and GlyR antibodies rarely exhibit type 1 diabetes mellitus or other systemic autoimmune diseases, which are reported in up to 35% of SPS cases.[6] In our series, only 3 patients (7%) had a concurrent systemic autoimmune disease.[41] Prodromal viral infections are rarely reported as potential triggers of PERM with GlyR antibodies. Only 10 patients of this study had viral infections preceding PERM, including 2 with cutaneous varicella zoster and 1 with COVID-19.[36,38] A previous report of encephalitis after West Nile virus infection[42] has to be interpreted with caution, because GlyR antibodies were tested only in serum, and the significance of serum GlyR antibodies remains uncertain, given their presence across a wide range of neurologic disorders.[12]

A notable feature of PERM with GlyR antibodies is the rapid onset of symptoms, with patients typically requiring hospital admission within a median of 2 weeks. The most common presenting symptoms indicated brainstem involvement mainly dysphagia, trismus, ptosis, and diplopia. When trismus occurred with rigidity and painful muscle spasms, tetanus was usually considered in the differential diagnosis.[24,26] The combination of trismus and diplopia may also mimic paraneoplastic brainstem encephalitis with Ri (anti-neuronal nuclear antibody type 2) antibodies, particularly when accompanied by laryngospasm and stridor.[43]

Other less common but characteristic presenting symptoms included diffuse or patchy dysesthesias, as well as cacosmia with dysgeusia. Dysesthesias were usually described as itching or pruritus and frequently associated with stiffness and muscle spasms. Although described previously,[39] itching/pruritus was more common among patients identified in our database (Table 1). The dysesthesias did not follow a particular nerve territory and could potentially be caused by the effect of GlyR antibodies on glycinergic neurotransmission, which plays an important role in pain and hyperalgesia at the level of brainstem somatosensory centers and dorsal horn of the spinal cord.[44]

Two of our patients had cacosmia and dysgeusia, as presenting symptoms not previously described in PERM. In the rat brain, glycine receptors are involved in sensory processing at the level of the olfactory bulb, retina, auditory, and vestibular nuclei.[45] Therefore, it is plausible that GlyR antibodies

Table 2 Demographic and Clinical Data of 19 Patients With PERM and GlyR Antibodies Reported in the Literature

Patient Age/sex[ref]	Presenting symptoms	PERM triad[a]	Immunotherapy	mRS score before/after treatment	Maintenance immunotherapy (mo)	Relapses (mo of follow-up)	Last mRS score (mo of follow-up)
23. 54/M[9]	Spontaneous and stimulus-induced myoclonus and left flank paresthesias	Yes, at follow-up	IVIG, IVMP, PLEX, CTX	5/3	No	Yes (14)	3 (24)
24. 49/M[24]	Painful spasms of the R leg, L arm stiffness, trismus, dysphagia, hyperhidrosis, and urinary retention	Yes, at admission	PLEX, oral prednisone	5/0	Prednisone (5)	No	0 (21)
25. 58/M[25]	Spontaneous and stimulus-induced myoclonus, and limb rigidity	Yes, at admission	PLEX, oral prednisone	4/1	Prednisone (18)	Yes (18)	0 (>24)
26. 39/M[26]	Trismus (isolated x 7 days); later dysphagia, R facial paresis, R leg stiffness, and myoclonus	Yes, at admission	IVIG, IVMP, PLEX, RTX	4/<3[b]	No	No	<3[b] (>12)
27. 66/F[27]	Dysesthesia in L cheek, nostril, and ear; 3 wk later, ophthalmoparesis and gait ataxia	Yes, at follow-up	IVIG, PLEX	5/5	No	No	4[c] (34)
28. 40/M[28]	Respiratory distress, myoclonus, hallucinations, dysphagia	Yes, at follow-up	IVIG, PLEX, prednisone	5/4	Prednisone (11)	Yes (7)	4 (12)
29. 47/M[29]	Myoclonus and diplopia, for 3 wk	Yes, at follow-up	IVIG, IVMP, PLEX, RTX	5/4	No	No	3 (24)
30. 60/M[30]	Rigidity and stimuli-sensitive muscle spasms in both legs for several mo; later dysphonia and diffuse pruritus	Yes at admission	PLEX, oral prednisone	4/3	Prednisone (12)	No	1 (12)
31. 41/M[31]	Respiratory distress, dizziness, and L facial palsy; a few d later, muscle stiffness and myoclonus	Yes, at admission	IVIG, IVMP	5/4	No	No	2 (24)
32. 60/M[32]	Respiratory distress, dysphagia, and dizziness for 1 wk; later diplopia, myoclonus	No, never stiffness	IVMP, PLEX	5/6	NA	NA	6 (2)
33. 46/M[33]	R Facial numbness and spasms and trismus; 2 wk later, diplopia and L arm stimulus-sensitive myoclonus	No, never limb rigidity	IVIG, IVMP, PLEX	4/1	Prednisone (24), AZA (24)	No	0 (36)
34. 61/M[34]	L Facial palsy and ptosis; 5 d later, rigidity and myoclonus in L leg	Yes, at admission	IVIG, IVMP	5/4	Prednisone (?), mycophenolate (12)	No	4 (16)
35. 65/M[35]	Dysphagia and hypoglossal nerve palsy; two wk later, diplopia and L facial paresis	Yes, at follow-up	IVIG, IVMP, PLEX	5/4	No	No	3 (18)
36. 75/M[36]	Painful muscle spasm with rigidity, dysarthria, dysphagia	Yes, at admission	IVIG, IVMP	5/6	NA	NA	6 (2)
37. 72/M[37]	Weakness of the tongue, trismus, dysphagia, dysarthria, and painful face spasms	Yes, at follow-up	IVIG	4/4	IVIG (6)	No	6 (12)
38. 65/M[38]	Dysphagia and agitation; 7 d later, left facial palsy and ophthalmoparesis	Yes, at follow-up	IVIG, IVMP, PLEX, RTX	5/6	NA	NA	6 (5)
39. 33/F[39]	Paresthesia in R face that spread to involve both legs along with stiffness around the trunk and abdomen over 6 mo	Yes, at admission	IVMP, PLEX, RTX	4/2	RTX (24)	No	2 (24)
40. 43/F[40]	Lower limb stiffness and spasms, myoclonus, and dysphagia	Yes, at admission	IVIG, IVMP, PLEX, RTX	4/3	IVIG (12), RTX (18), prednisone (10)	No	2 (18)
41. 16/M[41]	Intermittent hyperesthesia in the torso and legs, diplopia, and ptosis; weeks later, mild dysarthria, dysphagia, tongue and neck stiffness, and stimulus-sensitive myoclonus	Yes, at admission	IVIG	3/2	No	Yes (12)	2 (18)

Abbreviations: AZA = azathioprine; IVIG = IV immunoglobulin; IVMP = IV methylprednisolone; NA = not assessable; PLEX = plasmapheresis; RTX = rituximab.
[a] Combination of brainstem symptoms, muscle stiffness, and myoclonus or muscle spasms.
[b] "Patient had a dramatic and sustained clinical response"; mRS score cannot be unambiguously defined.
[c] mRS score at the time the patient died of reasons not related to PERM.

targeting these regions may contribute to cacosmia, as well as the dizziness and visual symptoms (hallucinations, "visual snow") reported in other patients.[13,31]

The diagnosis of PERM with GlyR antibodies requires a high index of suspicion because not all patients develop a full-fledged syndrome and EMG studies may not show features of

Table 3 Clinical Symptoms at Admission

Symptom	N (%)
Brainstem	
Dysphagia	22 (54)
Diplopia	17 (41)
Supranuclear gaze palsy/nystagmus	12 (29)
Facial palsy/spasms	12 (29)
Dysarthria	12 (29)
Trismus	11 (27)
Tongue weakness/stiffness	9 (22)
Respiratory distress (central hypoventilation/laryngeal spasms)	11 (27)
Ptosis	6 (15)
Oculomotor nerve palsy	6 (15)
CNS hyperexcitability	
Limb stiffness/painful muscle spasms	26 (63)
Myoclonus not defined as hyperekplexia	19 (46)
Hyperekplexia	11 (27)
Dysautonomia	
Urinary retention/urgency	10 (24)
Constipation	7 (17)
Hyperhidrosis	9 (22)
Episodes of dysautonomia	7 (17)
Other	
Pruritus/dysesthesias	14 (34)
Mood change (e.g., depression and anxiety)	7 (17)
Hallucinations	4 (10)
Insomnia/diurnal hypersomnia	3 (7)
Cacosmia/dysgeusia	3 (7)

SPS or myoclonus. In this series, only 61% of patients exhibited the characteristic triad of brainstem symptoms, muscle stiffness and spasms, and myoclonus at admission. Notably, 12% never developed muscle stiffness during the clinical course. One might question whether the term PERM should apply to patients with an incomplete phenotype; however, in our view, reclassifying these cases under a different name would create unnecessary confusion and offer little clinical benefit, especially given that outcomes do not differ between patients with complete and incomplete presentations.

The clinical course of PERM with GlyR antibodies was not only rapid but also severe, with all but 1 patient reaching an mRS score ≥4 within days of admission and 50% requiring ICU admission, but immunotherapy was effective and 77% were improved at discharge. We did not observe that patients who received second-line therapies, mainly RTX, had a better short-term outcome. However, the retrospective design of the study limits the ability to determine the specific contribution of each individual drug to clinical improvement. The finding of older age and ICU admission as independent predictors of bad outcome is in line with the prognostic factors identified in other autoimmune encephalitides. Increased age and ICU admission were associated with worse neurologic outcomes in a series of 111 patients with GABABR encephalitis[46] while age was also identified as a negative prognostic factor in a study of 134 patients with LGI1 encephalitis.[47] ICU admission but not age was an independent variable included in the Anti-NMDA Receptor Encephalitis One-Year Functional Status Score that accurately predicts 1-year functional status in patients with anti-NMDAR encephalitis.[48]

Although our study identifies PERM with GlyR antibodies as a severe, rapidly evolving disorder, different from the more chronic course of classical SPS and PERM with GAD antibodies, we acknowledge several limitations. First, we excluded 5 patients with clinical features suggestive of PERM. The main reasons for exclusion were a chronic clinical course, more typical of SPS, and the presence of episodes of brainstem dysfunction or muscle stiffness that improved spontaneously (eTable 2). Second, GlyR antibodies are not exclusive to PERM; they have also been reported in patients with typical SPS, as well as in those who develop additional brainstem symptoms or myoclonus over the chronic course of the disease, often described as PERM or SPS plus variants.[14,49] Some patients were initially diagnosed with SPS and, after several years, experienced subacute episodes of brainstem dysfunction suggestive of PERM.[8] A possible explanation for why GlyR antibodies are associated with various disorders involving dysregulated inhibitory neurotransmission is that specific properties, such as antibody Fc interaction with innate immunity, may influence the clinical phenotype.[50]

Although there are patients with GlyR antibodies who develop a chronic, usually less severe, clinical course suggestive of PERM, our study indicates that most patients with PERM and GlyR antibodies have a rapid and severe presentation of symptoms mainly resulting from brainstem involvement. The disease is much more common in men and infrequently associates with other autoimmune disorders. These demographic and clinical features support classifying PERM with GlyR antibodies separately from SPS spectrum disorders, a distinction that is crucial for evaluating targeted therapies and investigating its underlying immunopathogenic mechanisms.

Acknowledgment

The authors thank all physicians who have contributed by providing clinical information on their patients.

Author Contributions

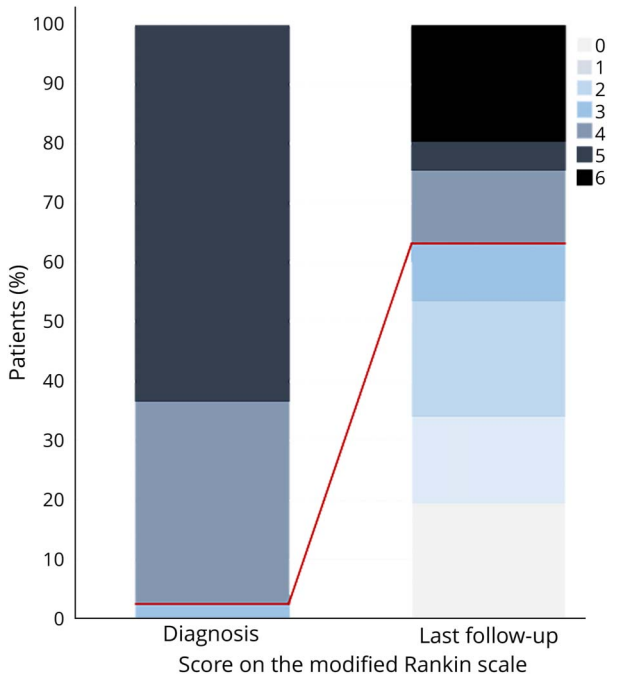
M. Guasp: drafting/revision of the manuscript for content, including medical writing for content; major role in the

Table 4 Clinical Features of Relapses

Patient	Maintenance therapy	Symptoms	Treatment	Outcome
1	No	Diplopia	Rituximab	Remission
5	Rituximab	Increased axial and leg stiffness	IVIG, prednisone	Remission
11	Azathioprine	Increased stiffness, myoclonus, respiratory function, and ophthalmoparesis	Immunoadsorption	Remission
15	Prednisolone, cyclosporine	Relapse of myoclonus and muscle spasms; increased stiffness	Increased doses of prednisolone and cyclosporine	Remission
17	Prednisolone, tacrolimus	Increased frequency of painful muscle spasms	Increased doses of prednisolone and IVMP	Remission
17	Prednisolone, tacrolimus	Increased frequency of painful muscle spasms	Increased doses of prednisolone and IVMP	Remission
18	Prednisolone, azathioprine	Relapse of ptosis and diplopia	IVIG and IVMP	Remission
18	Prednisolone, azathioprine	Relapse of ptosis and diplopia	IVMP and CTX	Remission
23	No	Worsening of gaze palsy, myoclonus, and stiffness	IVMP, CTX, and PLEX	Remission
25	No	Internuclear ophthalmoplegia	Prednisone and azathioprine	Remission
28	Prednisone	Recurrence of rigidity, myoclonus, and worsening of ophthalmoparesis	PLEX and increased doses of prednisone	Remission
41	No	Recurrence of ptosis, dysphagia, paresthesia, and tongue stiffness	IVIG	Remission

Abbreviations: CTX = cyclophosphamide; IVIG = IV immunoglobulin; IVMP = IV methylprednisolone; PLEX = plasmapheresis.

Figure 2 Functional Status Evaluated by the Modified Rankin Score (mRS) at Nadir and Last Follow-up



At nadir, 40 patients (97.5%) had a mRS score >3, whereas at the last follow-up, this figure decreased to 14 (34%).

acquisition of data; study concept or design; analysis or interpretation of data. A. Saiz: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. M. Ruiz-Vives: major role in the acquisition of data; analysis or interpretation of data. M. Almendrote: major role in the acquisition of data. J. Bruna: major role in the acquisition of data. J. González-Menacho: major role in the acquisition of data. J. Kaneko: major role in the acquisition of data. L. Martín-Aguilar: major role in the acquisition of data. F.A. Martínez-García: major role in the acquisition of data. K. Noda: major role in the acquisition of data. A. Ruiz Molina: major role in the acquisition of data. S. Sequeiros: major role in the acquisition of data. M.M. Simabukuro: major role in the acquisition of data. M. Takenaka: major role in the acquisition of data. M. Zurdo: major role in the acquisition of data. J.O. Dalmau: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. T. Iizuka: major role in the acquisition of data; analysis or interpretation of data. F. Graus: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

Study Funding

This study was funded by Instituto de Salud Carlos III (ISCIII)–Subdirección General de Evaluación y Formento de

la Investigación Sanitaria and co-funded by European Union, Fondo de Investigación Sanitaria (PI24/00899; M.G.) and Juan Rodés grant (JR23/00030; M.G.) from the ISCIII, Spain, which is co-financed by Fondo Social Europeo Plus.

Disclosure

J. Dalmau receives royalties from Athena Diagnostics for the use of Ma2 as an autoantibody test and from Euroimmun for the use of NMDA, GABAB receptor, GABAA receptor, DPPX, and IgLON5 as autoantibody tests and has received an unrestricted research grant from Euroimmun. F. Graus holds a patent licensed to Euroimmun for the use of IgLON5 in an autoantibody test, for which he receives royalties and receives honoraria from MedLink Neurology for his role as associate editor. The other authors report no relevant disclosures. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/NN.

Publication History

Received by *Neurology® Neuroimmunology & Neuroinflammation* May 29, 2025. Accepted in final form July 7, 2025.

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