CLINICAL/SCIENTIFIC NOTE OPEN ACCESS

Progressive Encephalomyelitis With Rigidity and Myoclonus With Glycine Receptor and GAD65 Antibodies

Case Report and Potential Mechanisms

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Neurol Neuroimmunol Neuroinflamm 2024;11:e200298. doi:10.1212/NXI.0000000000200298

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Abstract

Objectives

Progressive encephalomyelitis with rigidity and myoclonus (PERM) is a severe form of stiff-person spectrum disorder that can be associated with antibodies against surface antigens (glycine receptor (GlyR), dipeptidyl-peptidase-like-protein-6) and intracellular antigens (glutamate decarboxylase (GAD65), amphiphysin).

Methods

We report clinico-pathologic findings of a PERM patient with coexisting GlyR and GAD65 antibodies.

Results

A 75-year-old man presented with myoclonus and pain of the legs, subsequently developed severe motor symptoms, hyperekplexia, a pronounced startle reflex, hallucinations, dysautonomia, and died 10 months after onset despite extensive immunotherapy, symptomatic treatment, and continuous intensive care support. Immunotherapy comprised corticosteroids, IVIG, plasmapheresis, immunoadsorption, cyclophosphamide, and bortezomib. Intensive care treatment and permanent isoflurane sedation was required for more than 20 weeks. CNS tissue revealed neuronal loss, astrogliosis and microgliosis, representing a pallido-nigro-dentato-bulbar-spinal degeneration pattern, specifically along GlyR and GAD expression sites. Neurons showed pSTAT1, MHC class I, and GRP78 upregulation. Inflammation was moderate and characterized by $CD8^+$ T cells and single $CD20^+/CD79a^+$ B/plasma cells. Focal tau-positive thread-like deposits were detected in gliotic brainstem areas. In the spinal cord, GlyR, glycine transporter-2, and GAD67 expression were strongly reduced.

Discussion

A possible potentiating effect of pathogenic GlyR antibodies together with T cells directed against neurons may have led to the severe and progressive clinical course.

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Go to Neurology.org/NN for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by the authors.

Introduction

Progressive encephalomyelitis with rigidity and myoclonus (PERM) is a potentially life-threatening immune-mediated disorder characterized by a dysfunction of the brainstem and spinal cord.[1-4] We present rare clinico-neuropathologic findings in a therapy-refractory PERM patient associated with glycine receptor (GlyR) and glutamic acid decarboxylase (GAD65) antibodies providing clues for pathomechanisms.

Case Report

A 75-year-old male patient presented with pain and myoclonus of the left leg. Brain and spine MRIs were unremarkable. He worsened within 2 months involving both legs, left leg extensor posturing, rhabdomyolysis, fluctuating vigilance, and psychomotor agitation. CSF cell count and protein levels were normal. Oligoclonal bands were negative. However, autoantibody screening in the serum and CSF was positive for GlyR antibodies (serum: 1:25, CSF: 1:10) (Figure 1A) and high-titer GAD65 antibodies (serum: up to 57.454 IU/mL, CSF: >2000 IU/mL, ELISA) without evidence of intrathecal GAD65-antibody synthesis. Two years before onset, the patient developed late-onset diabetes mellitus with low-level GAD antibodies (55.8 IU/mL). Immunotherapy with methylprednisolone, IV immunoglobulin, methotrexate, and cyclophosphamide showed no clinical improvement. Electroencephalography showed diffuse abnormalities without epileptiform discharges. Repetitive PET-CTs and further diagnostics showed no malignancies or cerebral hypometabolism/hypermetabolism. Owing to severe dysautonomia, an excessive startle reflex, hallucinations, spasms, myoclonus, and paraparesis, intensive care therapy was initiated 3 months after onset. Despite plasmapheresis and tryptophan immunoadsorption, an increase of sedative medication was necessary. Long-term inhalative sedation with continuous high-dose isoflurane for 5 months was required to achieve sufficient control of dysautonomia and motor hyperexcitability (Video 1). Weaning attempts led to symptom worsening. Immunotherapy with bortezomib showed no effect. After adding intrathecal baclofen, dronabinol, and tiapride treatment, isoflurane sedation could be replaced by IV sufentanil, propofol, dexmedetomidine, and diazepam. Follow-up cerebral MRI compared with 4 months earlier revealed generalized brain atrophy and pronounced bilateral, symmetric hyperintensities of the putamen, substantia nigra, nucleus ruber, and an olivary pseudohypertrophy (Figure 1, B and C). Correspondingly, affected CNS regions seen afterward in neuropathology are schematically visualized in coronal sections in Figure 1D. The patient remained in a comatose state without gag reflex, was continuously ventilated, showed persisting limb rigidity and myoclonus, and died 10 months after onset due to acutely decompensated cardiomyopathy. No tumor was found at autopsy.

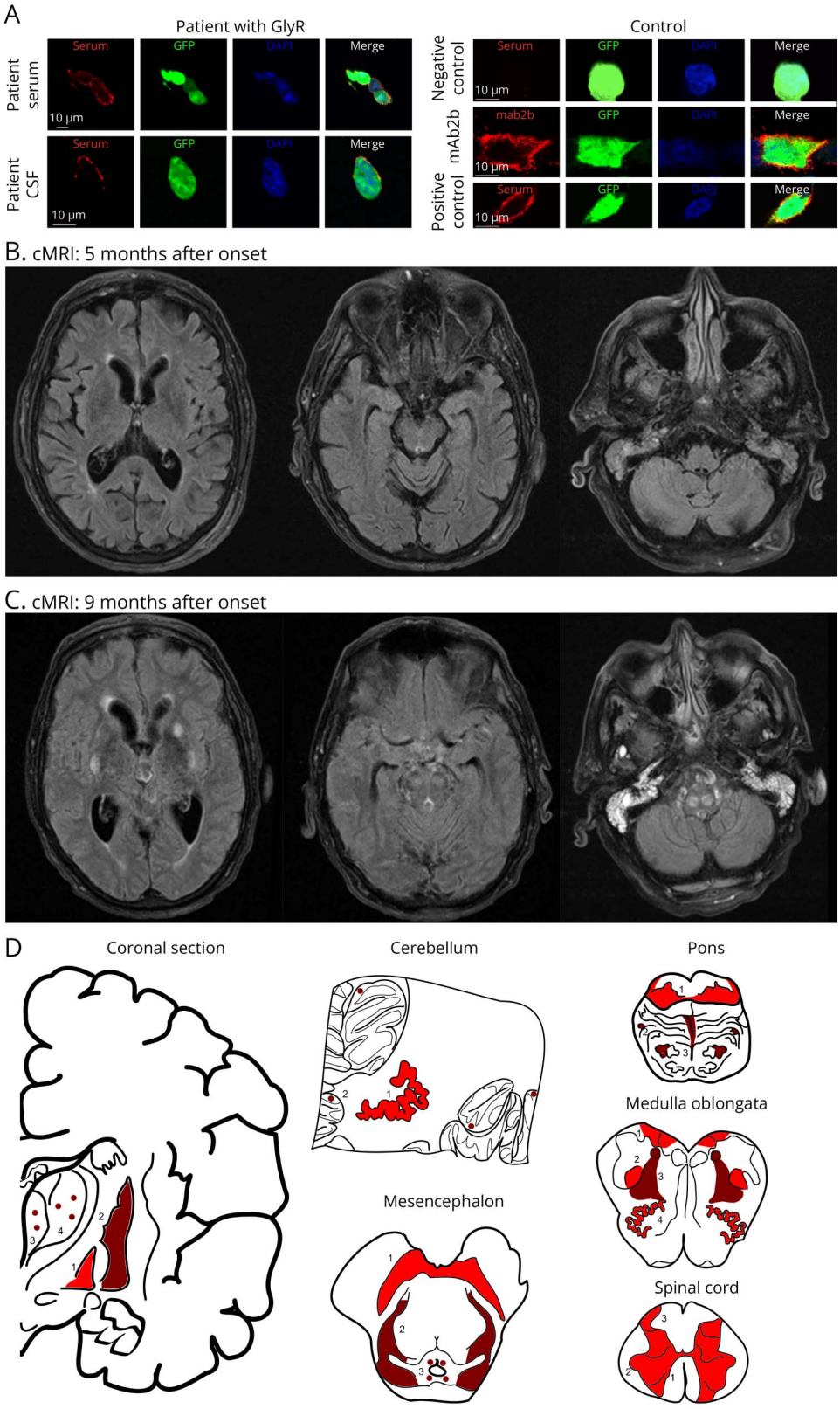
Postmortem histopathology revealed prominent neuronal loss, astrogliosis, and HLA-DR$^+$ microglial activation. The internal globus pallidus was more prominently affected than caudal parts of the posterior putamen, caudate nucleus, hypothalamus, and anterior thalamus (Figure 2A). The subthalamic nucleus was relatively well preserved compared with the affected colliculi, periaqueductal gray, and substantia nigra pars compacta (Figure 2B). The medulla oblongata was severely involved, affecting the respiratory group, the dorsal motor nucleus of the vagal nerve, reticular nuclei, and the trigeminal region (Figure 2B). The cerebellar dentate nucleus showed prominent axonal swellings, grumous degeneration, and rarefaction of the hilus (Figure 2C), whereas the cortex showed mild segmental Purkinje cell loss. Posterior and anterior horns of the spinal cord showed neuronal loss, chromatolytic neurons, microglial activation, and axonal swellings (Figure 2D). Affected regions were predominantly sites with high GAD and GlyR expression, while the hippocampus with high GAD but less intensive GlyR immunoreactivity was better preserved.[5]

Inflammation was moderate, widespread, and characterized by parenchymal and perivascular CD3$^+$/CD8$^+$granzymeB$^+$ T cells, single CD4$^+$ T cells, meningeal CD20$^+$/CD79a$^+$ B/plasma cells, and a diffuse neuronal cytoplasmatic IgG1 (but not IgG4) staining in affected regions, without C9neo complement deposits. HLA-DR$^+$–activated microglia was prominent particularly in pontine nuclei, anterior horn of the spinal cord, cerebellar dentate nucleus, globus pallidus, and medial substantia nigra. GFAP$^+$ reactive astrocytes were diffusely prominent. pSTAT1 was strongly positive in nuclei of cell types including neurons and locally attached T cells within the basal ganglia and cerebellum. Neurons showed MHC class I upregulation in the affected globus pallidus, cerebellar dentate nucleus, inferior olivary nucleus, dorsal motor nucleus of the vagal nerve, hypoglossal and vestibular nuclei, reticular formation nuclei, nucleus ambiguus, and substantia nigra. Glucose regulated protein-78 (GRP78), a marker for endoplasmatic reticulum stress, was strongly expressed in these neurons. The dorsal root of the spinal cord and its proximal peripheral nerves were infiltrated by single CD4$^+$, CD8$^+$ T cells and CD20$^+$/CD79a$^+$ B/plasma cells (eFigure 1, A–S).

Immunohistochemistry of neurodegeneration-associated protein aggregates revealed fine, tau-positive thread-like deposits (tAT8) in the affected dorsal medulla oblongata with the dorsal vagal and solitary nuclei (eFigure 1T). α-synuclein (eFigure 1U), β-amyloid, FUS, phTDP43, and p62 were negative (data not shown).

Expression of the GlyR (mAb4a), glycine transporter 2 (GlyT2), and GAD67 (rabbit-mAb) were significantly reduced in remaining neurons along the neuronal soma and dendrites of the ventral and dorsal horn of the spinal cord in PERM (Figure 3, A and B), compared with age-matched controls (Figure 3, C and D; Figure 2 second column and insets), while immunoreactivity of other receptors such as GABA(A)R and 5-HT7R appeared regular (eFigure 2). Hippocampal GAD67 expression was as high as in controls.

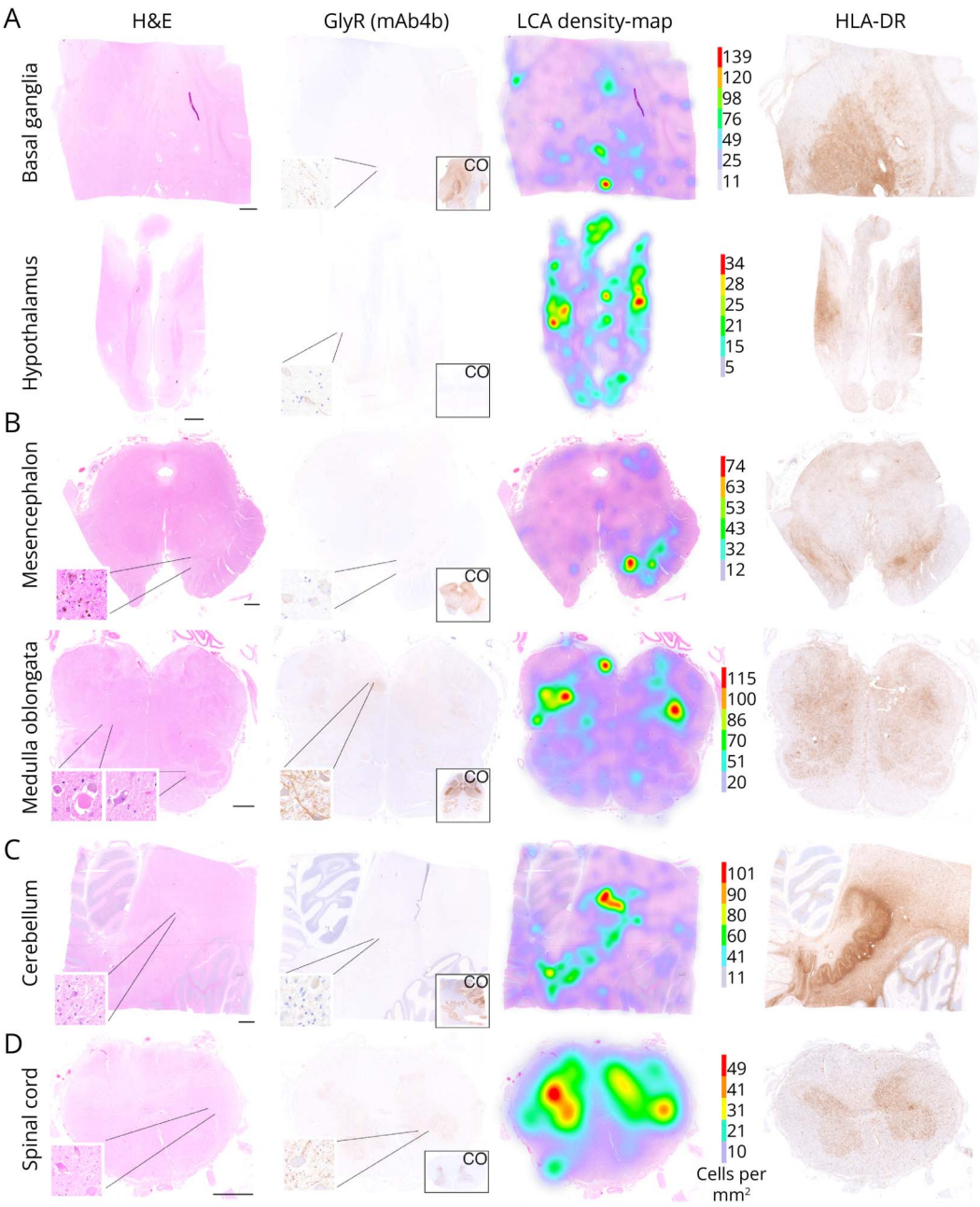
Figure 1 Cell-Based Assays, MRI Findings, and Lesion Map of the Patient With PERM



(A) Anti-GlyR antibodies were detected in cell-based assays in the patient's serum (1:25) and CSF (1:10) in a pattern comparable with positive controls shown (mAb2b = antibody specific for GlyR α1, dilution 1:500; positive control = other SPS patient with GlyR autoantibodies, serum dilution 1:50), but not in the negative control (= healthy person, serum dilution 1:50). (B) Brain MRI (FLAIR/T2-weighted images) of the patient performed 5 months after symptom's onset showed no significant abnormalities. (C) Follow-up MRI after 9 months showed brain atrophy, periventricular hyperintensities, edema of the basal ganglia and gliotic putamina, signal alterations within the mesencephalon involving the substantia nigra and nucleus ruber, and a degenerative olivary pseudohypertrophy in the medulla oblongata. (D) Respectively, lesion maps visualize severely (bright red), moderately (dark red), and mildly (dark red dots) affected CNS regions regarding neuronal loss, microglial activation, and inflammation in coronal sections through the right brain hemisphere at the level of the posterior basal ganglia in the coronal section (1: globus pallidus, 2: putamen, 3: nucleus caudatus, 4: thalamus), cerebellum (1: dentate nucleus, 2: cerebellar cortex), mesencephalon (1: substantia nigra, 2: reticular formation, 3: periaqueductal gray), pons (1: reticular formation, 2, 3: pontine nuclei), medulla oblongata (1: dorsal motor nucleus of the vagal nerve and solitary nuclei, reticular formation, 2: nucleus ambiguus, 3: reticular formation and trigeminal region, 4: inferior olivary nucleus), and spinal cord (1: ventral horn, 2: lateral horn, 3: dorsal horn). PERM = progressive encephalomyelitis with rigidity and myoclonus.

Data can be made available from the corresponding authors on reasonable request and after approval from the ethics review board at the Medical University of Vienna and Jena University Hospital. The study was approved by the Institutional Review Board of the Medical University of Vienna (EK 1123/2015 and 1636/2019) and Jena

Figure 2 CNS Pattern of Neuronal Loss and Inflammation in PERM



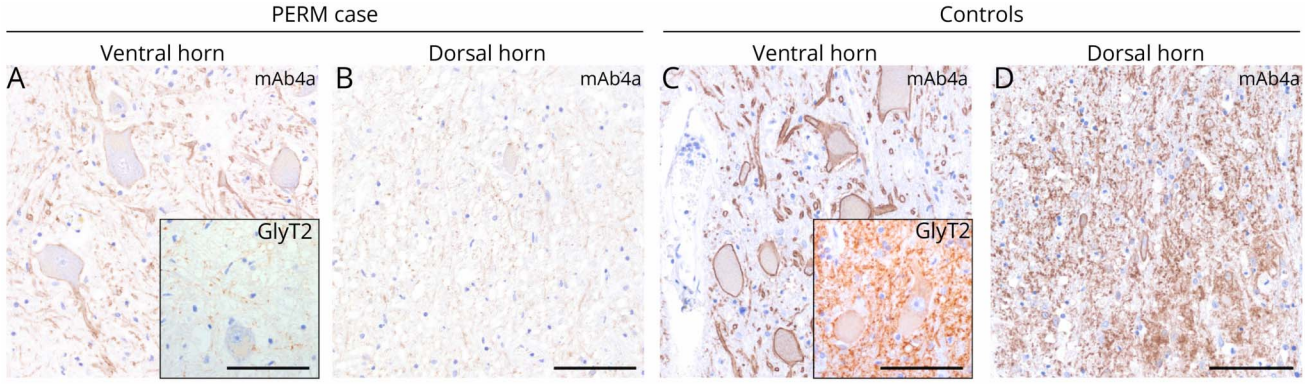
Tissue damage and inflammation predominantly affected GlyR-rich CNS regions, following a pallido-nigro-dentato-bulbar-spinal degeneration pattern: globus pallidus and hypothalamus (A), substantia nigra and nuclei within the medulla oblongata and reticular formation (B), cerebellar dentate nucleus (C), and the ventral and dorsal horn of the spinal cord (D). Neuronal loss and gliosis with chromatolytic neurons, single vacuolized neurons, and axonal spheroids (first column with details in boxes; H&E) were detected particularly in GlyR dense areas (second column with details and controls [CO] in boxes; GlyR immunohistochemistry [IHC]). Neuronal GlyR (mAb4a) expression was reduced in the ventral and dorsal horn of the spinal cord, compared with 2 age-matched controls (D, showing one control; see details in Figure 3, C and D). Inflammatory infiltrates were spatially and quantitatively (cells per mm^2) visualized by overlaying density maps of IHC with leucocyte common antigen (LCA) and respective H&E-stained sections (third column). QuPath Version 0.3.2 was used to perform positive cell detection of LCA/CD45-positive immune cells. Gaussian-weighted density maps were produced to visualize and quantify positive cells with color codes. These areas showed the highest average amount of immune cells per mm^2 (including focal maximum): medulla oblongata, 16.06 (115, close to nucleus ambiguus); spinal cord, 14.32 (49, dorsal horn); basal ganglia, 12.99 (139, globus pallidus); pons, 12.32 (179, nuclei in tegmentum and basis); cerebellum, 11.71 (101, dentate nucleus); mesencephalon, 5.33 (74, medial substantia nigra); and lateral substantia nigra, (37). HLA-DR^+ microglial activation was prominent in affected regions and correlated well with tissue damage and LCA positivity (fourth column). Scale bars: 2 mm. PERM = progressive encephalomyelitis with rigidity and myoclonus.

University Hospital. Written informed consent for publication of the clinical presentation through video of the deceased patient was obtained from the relative of the patient.

Discussion

Neuropathologic findings in our PERM case associated with GlyR and GAD65 antibodies followed a pallido-nigro-

Figure 3 Characterization of Immunohistochemical GlyR Expression in PERM



IHC expression of GlyR (mAb4a) and GlyT2 was reduced in the ventral and dorsal horn of the spinal cord in PERM (A–B), compared with age-matched controls (C–D). Scale bars: 100 µm. PERM = progressive encephalomyelitis with rigidity and myoclonus.

dentato-bulbar-spinal degeneration pattern that correlated well with clinical symptoms and neuroimaging.

The coexistence of a GlyR- and GAD65-directed immunoreaction may have determined the patient's clinical phenotype. On the one hand, we found aspects of a T cell–mediated process with upregulation of MHC class I and neurons surrounded by cytotoxic $CD8^+$ T cells showing pSTAT1 upregulation, creating a proinflammatory cytotoxic environment.[6,7] On the other hand, significantly reduced expression of the GlyR and GlyT2 on neurons most likely result from GlyR antibodies. A possible potentiating effect of GlyR-antibodies together with T cells attacking neurons and axons may have led to the unusually severe and progressive clinical course.

Pathogenic effects of GlyR antibodies include receptor internalization, functional blocking, and disruption of inhibitory Cl^- currents.[1,4,8,9] Autoantibodies target the GlyR α1-subunit of the most abundant heteromeric α1β GlyR in the adult CNS, which is particularly expressed in the spinal cord, brainstem, and cerebellum.[5] Previous neuropathologic PERM descriptions with unknown antibody status also showed neuronal loss, gliosis, demyelination, and perivascular lymphocytes primarily in the brainstem and spinal cord.[2,10-12] We observed that the GlyR and GlyT2 expression was significantly reduced in the spinal cord neurons, suggesting deleterious antibody effects. Intriguingly, variations in the presynaptic GlyT2 gene SLC6A5 were also shown to cause hyperekplexia.[13] We found only few $CD20^+/CD79a^+$ B/plasma cells mainly within the meninges, but not in the brain parenchyma, possibly due to the extensive immunotherapy. In contrast to in vitro results, we did not detect complement deposits.[4]

Of interest, the solitary nucleus and pallidum, both regions with prominent neuronal loss and microglia activation, revealed delicate tau-positive threads. Homeostatic and metabolic disturbances in affected neurons could be triggered by ongoing focal inflammation or a state of hyperexcitability due to the missing glycinergic input, leading to neurodegenerative processes and tau deposits over time.[8,14]

Clinically, sufficient control of spasticity and myoclonic jerks using high-dose isoflurane sedation was striking and may be explained by its depressant effect on the ventral horn of the spinal cord, as shown in a rat model.[15] Prominent injury to pontine nuclei might have caused the excessive startle reflex in our patient.[1,4,9]

In conclusion, antigen-directed T cell–mediated and antibody-mediated pathomechanisms may have led to reduced inhibitory neurotransmission, subsequent neuronal dysfunction, and cell death particularly in GlyR-rich and GAD-rich areas, despite extensive immunotherapy. Acknowledging the limitations of a single case, postmortem brain tissue, and the interpretation of immunohistochemical results, neuropathologic studies are very rare and may be of great value. We consider that our findings provide new insights into the pathogenesis and clinical peculiarities of PERM, contributing to guiding future studies and therapies.

Acknowledgment

The authors express our gratitude and thank the family of the deceased for giving the permission of presenting the patient's video. The authors particularly thank our coworkers at the Division of Neuropathology and Neurochemistry, Department of Neurology, Medical University of Vienna for their technical support.

Study Funding

This work was funded by grants from the Austrian Science Fund FWF, DOC 33-B27 (MW and RH), P 34864-B (JB), and I 6565-B (SYNABS; RH), the German Research Foundation (FOR3004; GE2519/8-1 and 9-1 to CG and VI586/11-1 and 12-1 to CV), the German Federal Ministry of Education and Research (01 GM1908B to CG), the Schilling Foundation (to CG), the Interdisciplinary Center of Clinical

Research Jena (IZKF) (to JW), and the Center of Rare Diseases Jena.

Disclosure

R. Höftberger reports speaker's honoraria from Novartis, UCB, and Biogen. C. Geis received speaker's honoraria and consultation fees from Roche, Sobi, and Alexion. The Medical University of Vienna (Austria; employer of R. Höftberger) receives payment for antibody assays and for antibody validation experiments organized by Euroimmun (Lübeck, German). A. Günther received speaker's honoraria from Boehringer Ingelheim, Daichii Sankyo, Pfizer, and Ipsen as well as research grants from MERZ Pharma and IPSEN. The other authors declare that they have no conflict of interest. Go to Neurology.org/NN for full disclosures.

Publication History

Received by *Neurology: Neuroimmunology & Neuroinflammation* March 11, 2024. Accepted in final form June 28, 2024. Submitted and externally peer reviewed. The handling editor was Editor Josep O. Dalmau, MD, PhD, FAAN.

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