Clin. Lab. 2026;72:XXX-XXX

CASE REPORT

Potential Pathogenic Role of Glycine Receptor α1 Autoantibodies in Sporadic Creutzfeldt-Jakob Disease

Hongquan Wu [1], Xin Kang [2], Chuan Hu [2], Changqing Zhou [2]

[1] *Department of Internal Medicine, Bishan Hospital of Chongqing, Sanhe Hospital, Chongqing, China*
[2] *Department of Neurology, Bishan Hospital of Chongqing Medical University, Chongqing, China*

ABSTRACT

Background: **Creutzfeldt-Jakob Disease (CJD) is a rare and fatal human neurodegenerative disorder, with sporadic CJD (sCJD) being the most common form. sCJD is characterized by rapidly progressive dementia, myoclonus, visual disturbances, cerebellar ataxia, pyramidal or extrapyramidal dysfunction, and akinetic mutism. The precise pathophysiology of sCJD remains incompletely understood, and there are currently no effective treatments or therapeutic strategies to halt disease progression.**
Methods: **In this case, we present a 63-year-old patient exhibiting rapidly progressive cognitive decline, visual disturbances, myoclonus, hypertonia, and ataxia. The diagnosis of sCJD was confirmed based on brain magnetic resonance imaging (MRI) findings and cerebrospinal fluid analysis.**
Results: **Serum analysis identified the presence of glycine receptor α1 (GlyRα1) immunoglobulin G (IgG) antibodies.**
Conclusions: **The clinical manifestations were consistent with typical symptoms of sCJD, raising the hypothesis that GlyRα1 autoantibodies contribute to the pathogenesis of sCJD.**
(Clin. Lab. 2026;72:xx-xx. DOI: 10.7754/Clin.Lab.2025.250810)

Correspondence:
Changqing Zhou
Department of Neurology
Bishan Hospital of
Chongqing Medical University
No. 9 Shuangxing Avenue
Bishan District, Chongqing 402760
China
Phone: +86 15825905085
Email: evsokanme@163.com

Case Report accepted August 20, 2025

KEYWORDS

sporadic Creutzfeldt-Jakob disease, glycine receptor, autoantibodies, movement disorders

LIST OF ABBREVIATIONS

CJD - Creutzfeldt-Jakob Disease
sCJD - sporadic Creutzfeldt-Jakob Disease
GlyRα1 - Glycine Receptor α1
GlyRs - Glycine Receptors
EEG - Electroencephalogram
CDC - Chinese Center for Disease Control and Prevention
MRI - Magnetic Resonance Imaging
CSF - Cerebrospinal Fluid
IgG - Immunoglobulin G
PERM - Progressive Encephalomyelitis with Rigidity and Myoclonus
SPS - Stiff Person Syndrome
CNS - Central Nervous System

OPL - Outer Plexiform Layer
IPL - Inner Plexiform Layer

INTRODUCTION

Creutzfeldt-Jakob Disease (CJD) is a rapidly progressive, rare, infectious, and universally fatal neurodegenerative disorder caused by prions, making it the most prevalent prion disease in humans. The estimated incidence is approximately 1 - 2 cases per million population annually, with the majority of patients succumbing within one year of clinical onset. CJD is classified into three categories: sporadic, genetic, and acquired. Among these, sporadic CJD (sCJD) constitutes the most prevalent form (approximately 85 - 90% of cases) [1]. The clinical manifestations of sCJD include rapidly progressive cognitive decline, myoclonus, visual disturbances, cerebellar ataxia, pyramidal or extrapyramidal dysfunction. The exact etiology and pathogenesis of sCJD remain incompletely understood, and no curative treatments currently exist. In this context, we report a case, in which glycine receptor α1 (GlyRα1) autoantibodies were detected, suggesting that these autoantibodies may play a role in the pathogenesis of sCJD.

CASE PRESENTATION

Initial condition at admission

The patient was a 63-year-old Han Chinese female with no significant medical history. Over the past month, she presented with blurred vision, followed by delayed responses, memory loss, and bradykinesia, all of which progressively worsened. Ten days before admission, the patient became unable to walk independently, leading to her hospitalization.

Physical examination

On examination, the patient was partially oriented with relevant responses. Muscle strength in the limbs was graded as 3/5. Muscle tone was normal, no pathological reflexes were observed, and meningeal irritation signs were negative.

Auxiliary examinations

Brain magnetic resonance imaging (MRI; enhanced)

Diffusion-weighted imaging showed hyperintensities in the bilateral caudate nuclei, anterior putamen, and parts of the bilateral cerebral cortical regions (Figure 1).

Laboratory tests

A cell-based indirect immunofluorescence assay was performed to facilitate the co-transfection of mammalian cells with plasmids encoding the antigen of interest and green fluorescent protein (GFP), with GFP serving as an internal control to confirm successful transfection. Final interpretation was based on the colocalization of GFP (green) and antibody (red) signals.

Using this method, we screened for a panel of neuronal surface autoantibodies (Table 1). Notably, the patient's serum tested positive for glycine receptor α1 (GlyRα1) IgG autoantibodies.

Additional tests for thyroid function, hepatitis B, HIV, syphilis, and other relevant infectious diseases showed no abnormalities.

Based on the patient's presentation and the initial suspicion of viral encephalitis, treatment with acyclovir was initiated, but the patient's symptoms continued to deteriorate during hospitalization, with progressive cognitive decline, worsening memory, slurred speech, increased muscle tone, and intermittent myoclonus. The myoclonic episodes remained resistant to treatment with valproic acid. Due to poor response to antiviral therapy, we sent cerebrospinal fluid and blood samples to the Prion Disease Laboratory at the Chinese Center for Disease Control and Prevention (CDC) for further testing. During the diagnostic evaluation, the patient's family chose to discharge her against medical advice. The subsequent test results from the Chinese CDC provided important diagnostic insights: The CSF 14-3-3 protein level was positive, and *PRNP* gene analysis revealed M/M polymorphism at codon 129 and E/E at codon 219, with no mutations associated with genetic CDJ. Two months later, the patient passed away. While a definitive diagnosis of CJD typically requires neuropathological confirmation (e.g., brain biopsy or autopsy), the family declined post-mortem brain examination. The Chinese CDC classified this case as probable sCJD. According to the U.S. CDC's 2018 criteria for diagnosing sCJD, this patient met the requirements for probable sCJD.

DISCUSSION AND CONCLUSION

In this patient, we detected GlyRα1 autoantibodies, a finding that was first reported in patients with progressive encephalomyelitis with rigidity and myoclonus (PERM) [2].

PERM is a severe form of Stiff Person Syndrome (SPS), a rare autoimmune neurological disorder characterized by progressive axial muscle rigidity, central nervous system hyperexcitability, and stimulus-sensitive painful muscle spasms [3]. While typical SPS often presents with milder symptoms and follows a chronic course with a generally favorable prognosis in the absence of complications, PERM is distinguished by rapid progression, severe myoclonus, muscle rigidity, and significant brainstem involvement. If left untreated, PERM can lead to death within weeks to months after the onset of rigidity symptoms, with a mortality rate reaching 40%. Subsequent studies have shown that GlyRα1 autoantibodies are present in the majority of PERM patients but are rarely found in typical SPS cases. Growing evidence suggests that the presence of GlyRα1 autoantibodies is a distinctive feature of PERM. The clinical manifestations of PERM can be attributed to the failure of inhibitory neurotransmission in the brainstem and spinal cord, which mirrors the consequences of genetic defects in

Table 1. Laboratory Tests.

	Serum analysis	Cerebrospinal fluid analysis
GlyRα1 IgG antibody	positive (+) 1:30	negative (-)
N-methyl-D-aspartate (NMDA) IgG antibody	negative (-)	negative (-)
α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor 1 (AMPA1) IgG antibody	negative (-)	negative (-)
AMPA2 IgG antibody	negative (-)	negative (-)
Leucine-rich glioma inactivated-1 (LGI1) IgG antibody	negative (-)	negative (-)
Contactin-associated protein-like 2 (CASPR2) IgG antibody	negative (-)	negative (-)
Gamma-aminobutyric acid B (GABAB) IgG antibody	negative (-)	negative (-)
Immunoglobulin-like domain containing 5 (IgLON5) IgG antibody	negative (-)	negative (-)
Dipeptidyl-peptidase-like protein-6 (DPPX) IgG antibody	negative (-)	negative (-)
Dopamine receptor D2 (DRD2) IgG antibody	negative (-)	negative (-)
Glutamic acid decarboxylase 65 (GAD65) IgG antibody	negative (-)	negative (-)
Metabotropic glutamate receptor 5 (mGluR5) IgG antibody	negative (-)	negative (-)
mGluR1 IgG antibody	negative (-)	negative (-)
Neurexin-3α-IgG	negative (-)	negative (-)

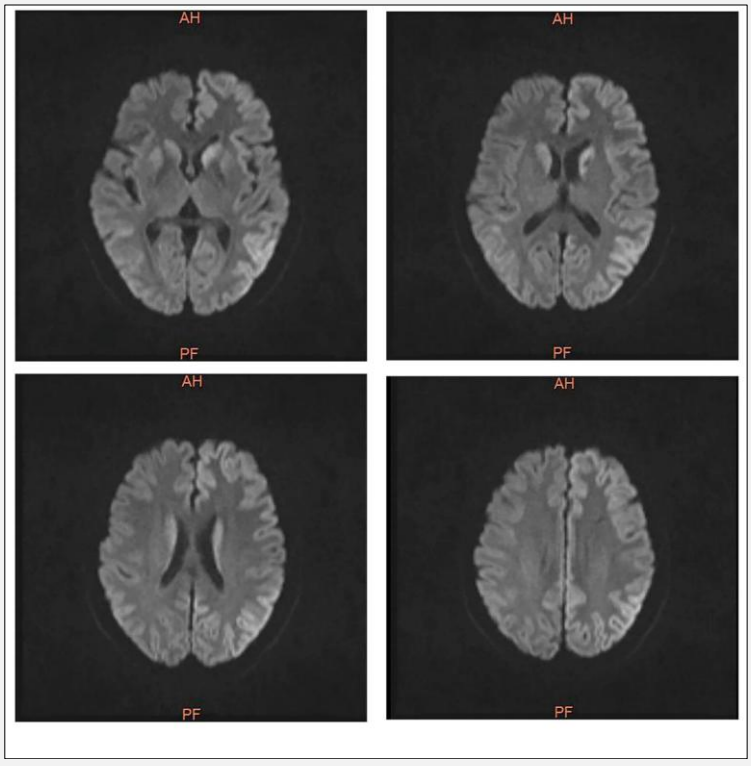

Figure 1. MRI of the patient's head after admission.

Diffusion-weighted imaging showed hyperintensities in the bilateral caudate nuclei, anterior putamen, and parts of the bilateral cerebral cortical regions.

glycinergic signaling [4-6].

Glycine, widely distributed throughout the mammalian central nervous system (CNS), functions primarily as an inhibitory neurotransmitter. It plays a significant role in regulating motor functions, sensory processing, and behavior control. Glycine exerts its effects through specific glycine receptors (GlyRs). In adult mammals, the α1-β heteromer represents the predominant GlyR subtype, with widespread expression throughout the CNS. Extensive biochemical, pharmacological, and genetic evidence indicates that adult glycinergic neurotransmission is primarily mediated by GlyRα1-β heteromers [6, 7].

Myoclonus, dystonia, and gait disturbances represent the most common movement disorders in patients with rapidly progressive prion disease. A longitudinal cohort study found that approximately 70% of patients with prion disease developed myoclonus. Myoclonus is a hallmark of sCJD and is the most prevalent motor abnormality, occurring in nearly all patients [8,9].

In transgenic mouse models with dominant mutations in the GlyRα1 subunit, disruption of glycinergic neurotransmission leads to the development of myoclonus [10]. Moreover, GlyRα1 autoantibodies in patients with autoimmune encephalitis have been shown to impair receptor function, resulting in myoclonus and muscle hypertonia [11]. Multiple clinical studies have demonstrated that in humans, GlyRα1 autoantibodies can induce myoclonus and increase muscle tone by impairing receptor function. In a cohort of patients with GlyRα1-IgG positivity, 47% exhibited cerebellar dysfunction or Parkinsonian syndromes during follow-up [12].

Previous studies have indicated that autoantibodies binding to GlyRs disrupt glycinergic neurotransmission, particularly in spinal motor neurons, by impairing glycinergic currents [6].

Visual impairment is also a significant clinical manifestation of sCJD, although its exact mechanism remains unclear. Multiple clinical studies have reported visual disturbances in patients with GlyRα1-IgG positivity [12]. Glycine serves as the primary inhibitory neurotransmitter in the retina, with all four α subunits of GlyR expressed at specific synapses in the retina. The GlyRα1 subunit, in particular, is found in both the outer plexiform layer (OPL) and inner plexiform layer (IPL), where it forms chemical synapses between AII amacrine cells, OFF-cone bipolar cells, and OFF-retinal ganglion cells. These synapses are crucial for transmitting scotopic signals via the OFF-channel pathway in the rod system [13].

In mouse models, glycine intake has been shown to improve memory and behavioral deficits. However, in clinical cases of sCJD, despite widespread cognitive decline, only a part of GlyRα1-positive patients exhibits cognitive dysfunction [4,6]. In a study of cognitive impairment among GlyRα1-positive patients, only one patient presented with dystonia, while others showed no motor disorders [14]. The underlying reasons for this discrepancy remain unclear, but they may involve regional differences in brain areas affected by antibodies or other unknown factors.

The clinical spectrum associated with GlyRα1 autoantibody-positive disorders shows substantial overlap with the core manifestations of sCJD. Importantly, no distinctive clinical features have been observed in either condition that are entirely absent in the other, suggesting potential mechanistic convergence. Previous reports have identified low titers of GlyRα1 autoantibodies in the serum of sCJD patients, and it has been proposed that these antibodies could, in theory, account for the full range of clinical features observed in sCJD [15]. However, the origin and pathogenic relevance of these antibodies remain unclear. They may be directly induced by the prion disease process or may arise secondarily due to prion-mediated neuronal destruction and subsequent release of neuronal antigens.

In addition, existing studies on *PRNP* genotypic subtypes in sCJD remain limited. According to the polymorphism at codon 129 of the *PRNP* gene, sCJD can be classified into distinct molecular subtypes. The present patient was homozygous for methionine at codon 129 (M/M genotype). However, whether the emergence of GlyRα1 autoantibodies in sCJD is modulated by PRNP genotype remains unknown.

In previously reported cohorts of GlyRα1 autoantibody-positive patients, a pattern of serum positivity with concurrent CSF negativity is frequently observed. The detection rate of GlyRα1 antibodies is significantly higher in serum than in cerebrospinal fluid [5], and patients with isolated serum positivity often present with a broader clinical spectrum. Although some studies have suggested that CSF testing may enhance diagnostic specificity, accumulating evidence supports the diagnostic utility of serum GlyRα1 antibody detection when clinical features are highly suggestive [12].

This study is limited by the lack of postmortem neuropathological confirmation and the absence of real-time quaking-induced conversion (RT-QuIC) testing, and thus the diagnosis remains clinical rather than definitive. Given the rarity of sCJD, its poorly defined pathophysiology, and the absence of disease-modifying therapies (with a near 100% fatality rate), further research is urgently needed. Future work will aim to systematically screen for GlyRα1 autoantibodies across sCJD patients with varying PRNP codon 129 genotypes to clarify underlying pathogenic mechanisms and assess the therapeutic relevance of this autoimmune response.

Informed Consent:

Written informed consent was obtained from participant.

Consent to Publish:

Written informed consent has been provided by the patient to have the case details and any accompanying images published.

Declaration of Interest:
We declare that we have no conflict of interest.

References:

1. Uttley L, Carroll C, Wong R, Hilton DA, Stevenson M. Creutzfeldt-Jakob disease: a systematic review of global incidence, prevalence, infectivity, and incubation. Lancet Infect Dis 2020;20 (1):e2-e10. (PMID: 31876504)

2. Hutchinson M, Waters P, McHugh J, et al. Progressive encephalomyelitis, rigidity, and myoclonus: a novel glycine receptor antibody. Neurology 2008;71(16):1291-2. (PMID: 18852446)

3. Dalakas MC. Therapies in Stiff-Person Syndrome: Advances and Future Prospects Based on Disease Pathophysiology. Neurol Neuroimmunol Neuroinflamm 2023;10(3):e200109. (PMID: 37059468)

4. Carvajal-González A, Leite MI, Waters P, et al. Glycine receptor antibodies in PERM and related syndromes: characteristics, clinical features and outcomes. Brain 2014;137(Pt 8):2178-92. (PMID: 24951641)

5. Martinez-Hernandez E, Ariño H, McKeon A, et al. Clinical and Immunologic Investigations in Patients With Stiff-Person Spectrum Disorder. JAMA Neurol 2016;73(6):714-20. (PMID: 27065452)

6. Crisp SJ, Dixon CL, Jacobson L, et al. Glycine receptor autoantibodies disrupt inhibitory neurotransmission. Brain 2019;142(11): 3398-410. (PMID: 31591639)

7. Dutertre S, Becker CM, Betz H. Inhibitory glycine receptors: an update. J Biol Chem 2012;287(48):40216-23. (PMID: 23038260)

8. Rodriguez-Porcel F, Ciarlariello VB, Dwivedi AK, et al. Movement Disorders in Prionopathies: A Systematic Review. Tremor Other Hyperkinet Mov (N Y) 2019;9. (PMID: 31871824)

9. Sequeira D, Nihat A, Mok T, et al. Prevalence and Treatments of Movement Disorders in Prion Diseases: A Longitudinal Cohort Study. Mov Disord 2022;37(9):1893-903. (PMID: 35841311)

10. Becker L, von Wegerer J, Schenkel J, Zeilhofer HU, Swandulla D, Weiher H. Disease-specific human glycine receptor alpha1 subunit causes hyperekplexia phenotype and impaired glycine- and GABA(A)-receptor transmission in transgenic mice. J Neurosci 2002;22(7):2505-12. (PMID: 11923415)

11. Kalampokini S, Motkova I, Bargiotas P, Artemiadis A, Zis P, Hadjigeorgiou GM. A case of unusual presentation with anti-glycine receptor (GlyR) and myelin oligodentrocyte glycoprotein (MOG) antibody. Clin Park Relat Disord 2023;8:100195. (PMID: 37091118)

12. Piquet AL, Khan M, Warner JEA, et al. Novel clinical features of glycine receptor antibody syndrome: A series of 17 cases. Neurol Neuroimmunol Neuroinflamm 2019;6(5):e592. (PMID: 31355325)

13. Wässle H, Heinze L, Ivanova E, et al. Glycinergic transmission in the Mammalian retina. Front Mol Neurosci 2009;2:6. (PMID: 19924257)

14. Hansen N, Bartels C, Stöcker W, Wiltfang J, Fitzner D. Impaired Verbal Memory Recall in Patients With Axonal Degeneration and Serum Glycine-Receptor Autoantibodies-Case Series. Front Psychiatry 2021;12:778684. (PMID: 35153852)

15. Angus-Leppan H, Rudge P, Mead S, Collinge J, Vincent A. Autoantibodies in sporadic Creutzfeldt-Jakob disease. JAMA Neurol 2013;70(7):919-22. (PMID: 23699783)