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CASE REPORT

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Ketamine for acute management of refractory stiff person syndrome: a case report

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Abstract

Background Stiff Person Syndrome (SPS) is a rare autoimmune neurological disorder characterized by progressive muscle rigidity and painful spasms. Standard treatments often yield variable responses, particularly in severe, refractory cases. This case report highlights the novel use of ketamine as an effective therapeutic agent for managing acute SPS exacerbations, underscoring its potential as a second-line treatment for patients unresponsive to conventional therapies.

Case presentation A 22-year-old male with SPS, diagnosed via anti-glycine receptor antibodies, presented with an acute exacerbation of symptoms, including severe stiffness triggered by sensory stimuli. Initial management with high-dose benzodiazepines, baclofen, and intravenous methocarbamol failed to provide adequate relief. The patient was subsequently treated with intravenous ketamine, resulting in rapid and significant symptom resolution. Despite initial improvement, the patient experienced multiple recurrent flares requiring repeated ketamine administration. Over time, ketamine proved consistently effective in resolving acute symptoms when standard treatments were insufficient. The patient's management was complicated by anxiety, hypoxia, venous thromboembolism, and other comorbidities, highlighting the need for a multidisciplinary approach.

Conclusions This case illustrates the potential utility of ketamine in managing acute and refractory SPS symptoms, providing rapid symptom resolution and reducing disease burden during severe flares. Ketamine's mechanism of action, including NMDA receptor antagonism and enhancement of GABAergic signaling, makes it a promising adjunct in SPS treatment protocols. This report emphasizes the importance of individualized, multidisciplinary care and the need for further research to establish ketamine's role in the long-term management of SPS.

Keywords Stiff person syndrome, Ketamine, Anxiety, Muscle rigidity, Pain management

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Background

Stiff Person Syndrome (SPS) is a rare autoimmune neurological disorder characterized by progressive muscle rigidity and painful spasms precipitated by sensory or emotional stimuli, with an estimated incidence of 1–2 per million [1]. Although the precise etiology of SPS is unknown, it is strongly associated with elevated anti-glutamic acid decarboxylase (anti-GAD65) antibodies which target the enzyme responsible for synthesizing gamma-aminobutyric acid (GABA) [2, 3]. Other notable antibodies include anti-amphiphysin, anti-glycine receptor, and anti-neuronal nuclear antibodies, which impair inhibitory neurotransmission and result in the hallmark hyperexcitability and rigidity of SPS [4].

SPS presents with a spectrum of phenotypes. The classic phenotype involves axial and proximal limb stiffness, progressing to painful spasms exacerbated by stimuli such as sound or touch [1]. Variants include stiff limb syndrome, which is localized to one limb, and SPS-plus, which includes classic symptoms along with cerebellar or brainstem dysfunction [1, 2]. Additionally, autoimmune disorders are frequently comorbid with SPS, and a significant proportion of patients also experience anxiety, which is likely exacerbated by disrupted GABAergic neurotransmission [2, 4].

Standard treatment involves enhancing GABAergic signaling using $GABA_A$ receptor agonists such as benzodiazepines and the $GABA_B$ receptor agonist, baclofen. Adjunct therapies include opioids for pain relief, antiseizure medications and immunomodulatory treatments such as intravenous immunoglobulin (IVIG), plasmapheresis, and rituximab [1, 5, 6]. However, therapeutic responses vary significantly, and there is no universally accepted protocol due to the rarity of the condition. This case focuses on a 22-year-old male with refractory acute SPS symptoms successfully managed with ketamine, emphasizing its potential role in treatment, and it highlights the importance of addressing comorbid anxiety in this patient population.

Case presentation

A 22-year-old male with a past medical history of anxiety and SPS, diagnosed in 2018 via positive anti-glycine receptor antibodies, initially presented with symptoms of progressive limb stiffness, episodic spasms triggered by sensory stimuli, and difficulties with ambulation. The patient described a history of flares triggered by sensory stimuli such as loud noises and bright lights, with this most recent flare triggered by exposure to a fire alarm.

The patient had no documented history of other autoimmune conditions, including autoimmune thyroid disease, type 1 diabetes mellitus, or celiac disease, which are known to co-occur with SPS. Upon presentation, the patient was treated with high-dose oral diazepam (30 mg), IV methocarbamol (1,000 mg every 8 h), and low doses of ketamine. Despite these interventions, his symptoms worsened, necessitating transfer to the intensive care unit (ICU) for high-dose ketamine administration. After administration of the high dose ketamine his symptoms partially improved and the patient was discharged on April 15, though he reported persistent anxiety and dissatisfaction with his care, feeling that he had not returned to baseline function.

On April 16, the patient returned via life flight with stiffness in his left side and right lower extremity. En route, he received two doses of ketamine (25 mg) followed by an additional 50 mg IV ketamine in the ED, resulting in complete symptom resolution. He was discharged the same day, ambulatory and asymptomatic.

However, two days later, on April 18, the patient presented again with stiffness that progressed to involve all limbs, along with chest tightness and shortness of breath. IV ketamine (50 mg) relieved his upper extremity symptoms, and he was admitted to the medical floor. During this admission, the patient declined benzodiazepines and fentanyl due to prior adverse effects but agreed to a regimen that included cyclobenzaprine (10 mg every 8 h), acetaminophen (975 mg TID), and as needed methocarbamol.

During his hospitalization, the patient developed several complications, including hypoxia (with oxygen saturation dropping to the 60s), a deep vein thrombosis (DVT) in his upper extremity related to the IV line, and a concussion resulting from a fall triggered by a flare. Imaging excluded significant head trauma and a pulmonary embolism. These complications, combined with escalating anxiety, contributed to the prolonged hospitalization. Anxiety was managed with hydroxyzine (50 mg), which provided some relief. By April 30, the patient's symptoms had improved, and he was discharged on a tapering regimen of hydromorphone and baclofen, along with prescriptions for oral clonazepam (0.5 mg) and hydroxyzine to help manage his anxiety.

For the next five months, the patient remained symptom-free while receiving biweekly IVIG therapy. However, in August 2024, due to side effects from IVIG, he transitioned to plasmapheresis which kept his symptoms at bay. Unfortunately, he discontinued this treatment after relocating to a new city.

On November 1, 2024, the patient experienced a flare triggered by environmental stressors in his new dorm room. He reported symptoms of twitching, weakness, and progressive stiffness affecting his neck, back, and all four extremities. Despite taking lorazepam (10 mg) at home, he did not experience relief and subsequently presented to the ED. IV lorazepam (8 mg) in the ED provided partial improvement, and upon admission, his treatment regimen was adjusted to include diazepam

Table 1 Summary of key events in the patient's clinical course

Date	Event	Interventions	Outcome
April 9, 2024	Initial presentation with acute flare triggered by fire alarm	Oral diazepam (30 mg), IV methocarbamol (1,000 mg every 8 h), low-dose ketamine; ICU transfer for high-dose ketamine	Partial symptom improvement; discharged on April 15 with persistent anxiety and dissatisfaction
April 16, 2024	Re-presentation with stiffness on the left side and right lower extremity	Life flight; ketamine (25 mg × 2 en route, 50 mg IV in ED)	Complete symptom resolution; discharged same day
April 18, 2024	Third presentation with stiffness in all limbs, chest tightness, and shortness of breath	IV ketamine (50 mg), cyclobenzaprine (10 mg every 8 h), acetaminophen (975 mg TID), as needed methocarbamol	Symptoms improved; hospitalized with complications including hypoxia, DVT, and concussion
April 30, 2024	Discharged following prolonged hospitalization	Tapering hydromorphone, baclofen, oral clonazepam (0.5 mg), hydroxyzine (50 mg)	Improved symptoms, anxiety partially managed
August 2024	Transition from IVIG to plasmapheresis due to side effects	Biweekly IVIG therapy switched to plasmapheresis	Symptom-free period until relocation
November 1, 2024	Flare triggered by environmental stressors in new dorm room	Lorazepam (10 mg at home), IV lorazepam (8 mg), diazepam (10 mg QID), baclofen (20 mg TID), IV fluids; later 50 mg IV ketamine in ICU	Symptoms resolved; discharged next day
November 3–4, 2024	Recurrence of symptoms	IV ketamine (50 mg each visit)	Symptom-free following treatment

(10 mg QID), Baclofen (20 mg TID), and IV fluids. As the pain and stiffness persisted, IV morphine (2 mg every 4 h) was trialed without significant improvement. The patient requested ketamine based on prior success, and after a transfer to the ICU, a 50 mg ketamine push resolved his symptoms entirely. He was discharged the following day, with follow-up arranged for neurology and plasmapheresis.

The patient returned on November 3 and 4 with recurrent flares, successfully treated each time with IV ketamine. Since the last episode, he has remained symptom-free.

In summary, the patient's clinical course, including key interventions and outcomes, is outlined in Table 1.

Discussion

This case report highlights the efficacy of ketamine in managing severe, refractory symptoms of SPS, a rare and debilitating neurological condition. The patient's recurrent flares and rapid resolution of symptoms with ketamine show its potential role as a therapeutic agent, particularly in acute exacerbations unresponsive to standard treatments.

The clinical course presented here aligns with known SPS triggers, including sensory stimuli and stress, and demonstrates the variability of therapeutic responses among patients [1]. While benzodiazepines and baclofen remain first-line therapies, their variable efficacy and potential adverse effects, exemplified by this patient's refusal to continue certain medications, illustrate the need for alternative treatment options [1]. The patient's dramatic response to ketamine highlights its potential as a second-line therapy or adjunctive treatment in SPS, particularly for patients with refractory symptoms or contraindications to standard regimens.

Ketamine's mechanism of action in SPS likely involves its N-methyl-D-aspartate (NMDA) receptor antagonism, which may counteract the hyperexcitability of the central nervous system caused by disrupted inhibitory neurotransmission [7]. While NMDA receptor antagonism is not a primary therapeutic target in SPS, excessive excitatory neurotransmission can contribute to muscle rigidity and spasms, making NMDA antagonism relevant in acute symptom control [8]. However, the primary mechanism of SPS pathophysiology involves impaired GABAergic inhibition. GABA is the main inhibitory neurotransmitter in the central nervous system, and autoantibodies against glutamic acid decarboxylase (GAD) in SPS patients lead to reduced GABA synthesis, resulting in neuronal hyperexcitability [8]. Enhancing GABAergic transmission is a key therapeutic approach, with benzodiazepines and baclofen being commonly used to increase GABAergic tone and reduce muscle rigidity and spasms [8]. Ketamine also enhances the function of GABA receptors, particularly in environments with low GABA concentrations, such as those found in SPS, which could help restore normal inhibitory signaling and reduce muscle rigidity [3, 9]. These mechanisms provides a plausible rationale for its efficacy, particularly in acute settings, where rapid symptom resolution is critical [6, 10]. Previous literature on ketamine use in SPS is limited, with most evidence derived from anecdotal reports or small case series [6, 10]. This case adds to the growing body of evidence supporting ketamine's role in managing SPS flares and highlights its utility in the emergency and critical care setting.

The safety profile of ketamine must also be considered. Short-term side effects include neuropsychiatric symptoms such as hallucinations, dissociation, and agitation,

which are usually transient and self-limited [11, 12]. Cardiovascular effects such as elevated blood pressure and heart rate are also common, along with gastrointestinal symptoms like nausea and vomiting [12–14]. In contrast, long-term ketamine use has been associated with more serious complications, including ulcerative cystitis, hepatobiliary dysfunction, cognitive impairment, and potential neurotoxicity [12, 15]. There is also a potential for tolerance development with repeated ketamine use, which could reduce its long-term efficacy [16]. While tolerance is a known complication of ketamine use, it is not well documented in the literature. In this case, the patient did not demonstrate a need for escalating doses over time. Ketamine maintained its efficacy across multiple acute episodes, suggesting that it may remain a viable option for intermittent flare management. However, further research is needed to assess the risks of tolerance with chronic ketamine use in SPS patients.

A related drug, esketamine (S(+)-ketamine) may also be of benefit as it has been shown to inhibit the desensitization of $GABA_B$ receptors which mitigates the development of tolerance to other treatments like baclofen, which is often used to manage spasticity in SPS [16]. Esketamine is the S-enantiomer of ketamine and has a higher affinity for the NMDA receptor, making it approximately four times more potent than the R-enantiomer [17]. Ketamine and esketamine have shown a similar efficacy in the treatment of depression, but esketamine is associated with a more favorable tolerability profile, with fewer cognitive disturbances and psychotomimetic effects compared to racemic ketamine [17]. Although esketamine has shown a more favorable tolerability profile in psychiatric conditions, there are currently no studies on its efficacy in SPS. Future research is necessary to explore whether esketamine could offer similar benefits with fewer side effects.

However, this case also underscores several limitations and challenges in managing SPS. First, while ketamine provided rapid relief, it does not address the underlying autoimmune pathophysiology of the disease. The patient's reliance on intermittent ketamine for symptom control raises concerns about long-term management strategies. Similar to its use in mood disorders, ketamine's effects in SPS appear to be temporary. In depression and anxiety disorders, ketamine provides rapid symptom relief through NMDA receptor antagonism and glutamate modulation but lacks long-term efficacy unless combined with adjunctive therapies [12]. Similarly, in SPS, ketamine's ability to restore excitatory-inhibitory balance may offer only transient relief, necessitating the use of additional immunomodulatory, symptomatic, and psychiatric treatments to sustain long-term improvement.

Second, the associated complications, including anxiety, hypoxia, and venous thromboembolism, demonstrate the multifaceted nature of SPS and the importance of a multidisciplinary approach to care [18]. Anxiety, in particular, likely contributed to the frequency and severity of flares, emphasizing the need for comprehensive psychiatric and psychological support in these patients [19].

The link between anxiety and SPS appears to involve the disruption of GABAergic signaling by autoantibodies [20]. Studies have demonstrated this link, showing that intrathecal application of IgG from SPS patients with anti-GAD antibodies, as well as anti-amphiphysin antibodies, induces anxiety-like behaviors in animal models [21, 22]. These findings suggest that such autoantibodies interfere with GABAergic signaling in brain regions associated with anxiety, including the amygdala and hippocampus, contributing to the development of anxiety in SPS [21, 22].

Clinical observations further support this association. A systematic review reported that anxiety is present in 56% of SPS cases, making it one of the most prevalent psychiatric symptoms in this patient population [19]. Similarly, SPS patients often attribute their anxiety and phobias to their neurological condition rather than viewing them as independent psychiatric disorders [23]. These findings highlight the contribution of autoantibody-mediated GABAergic dysfunction to anxiety in SPS and the importance of addressing anxiety as an important component of patient care.

Conclusion

This case highlights the importance of individualized, multidisciplinary care in managing SPS. Ketamine provided rapid and effective relief during acute exacerbations, demonstrating its potential in treating refractory cases. Further research is needed to determine optimal dosing, safety, and long-term efficacy of ketamine in SPS. Ketamine's role within a comprehensive treatment framework, including immunomodulation and psychiatric support for managing comorbid anxiety, requires further investigation. Ketamine is a viable treatment option in critical care settings for acute SPS flares, and addressing the psychological aspects of the disease is important for improving patient outcomes.

Abbreviations

SPS	Stiff Person Syndrome
GABA	Gamma-Aminobutyric Acid
anti-GAD65	Anti-Glutamic Acid Decarboxylase 65
IVIG	Intravenous Immunoglobulin
ED	Emergency Department
ICU	Intensive Care Unit
NMDA	N-Methyl-D-Aspartate
DVT	Deep Vein Thrombosis

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Author contributions
E.E. conceptualized the case report, collected patient data, and drafted the initial manuscript. W.K. assisted in data collection, contributed to the literature review, and supported manuscript writing. B.S. provided critical clinical insights, interpreted the patient's management strategies, and revised the manuscript for important intellectual content. L.L. supervised the clinical management of the patient, contributed to data interpretation, and reviewed the manuscript. N.G. and J.L. oversaw the patient's treatment during hospitalization, contributed to the discussion of therapeutic implications, and reviewed the manuscript for accuracy and clarity. All authors read and approved the final manuscript.

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Competing interests
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