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Intranasal midazolam for treating acute respiratory crises in a woman with stiff person syndrome

Giuseppe Cosentino, MD, PhD, Marcello Romano, MD, Margherita Algeri, MD, Filippo Brighina, MD, Enrico Alfonsi, MD, Cristina Tassorelli, MD, PhD, and Grazia Crescimanno, MD

Correspondence
Dr. Romano
mc.romano1958@gmail.com

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Video

Stiff person syndrome (SPS) is a rare neurologic disorder characterized by progressively worsening rigidity and spasms of the axial and limb muscles. Dyspnea has been recently recognized as a common symptom in SPS,[1] and life-threatening respiratory crises have been occasionally reported and suspected to be responsible for sudden death in these patients.[2,3] The pathophysiologic mechanisms of these respiratory manifestations remain unclear. Some authors have hypothesized that rigidity and/or spasm of the muscles of the trunk could prevent normal rib cage movements and excursion of the diaphragm.[1]

Here, we report the clinical history of a 55-year-old woman affected by SPS since about 10 years, presenting with crises of severe dyspnea in the past 2 years. The woman also bore several autoimmune comorbidities illustrated in table.

The clinical onset presented with stiffness of the trunk, with exaggerated lumbar lordosis and neck hyperextension, causing postural instability and progressively worsening difficulties in walking until wheelchair dependence. A few months after onset, diffuse painful muscle spasms, mainly induced by voluntary movements or precipitated by external stimuli, appeared in the proximal and distal muscles of the 4 limbs. Spasms slowly worsened over time, being responsible for repeated episodes of muscle and tendon tears. The clinical picture was completed by progressive urinary retention requiring bladder catheterization, likely due to urethral sphincter spasm,[4] myoclonic jerks of the abdominal and lower limb muscles, mainly triggered by the attempt to stand up, moderate dysphagia and, finally, acute respiratory crises. The respiratory crises were triggered by cough, laughter, or activities requiring increased respiratory efforts, and they were characterized by a sudden onset and severe dyspnea with mild desaturation (SpO_2 range of 85%–90%) as assessed by pulse oximetry. Neurologic examination was remarkable for hyperreflexia in all 4 limbs and positive bilateral Hoffman signs.

MRI examination of the brain and spinal cord was unremarkable. Paraneoplastic profiles were negative. Laboratory tests revealed positive antibodies against glutamic acid decarboxylase (4.7 U/mL, >1.0 U/mL positive), a common finding in subjects with SPS. The diagnosis of SPS was corroborated by electromyographic evidence of continuous motor unit activity in agonist and antagonist muscles, inconstant 3- to 4-Hz pseudorhythmic myoclonic EMG discharges in the lower limbs, and long-latency reflexes evoked by innocuous sural nerve stimulation in the lower limbs.

The patient was unsuccessfully treated with oral prednisone (0.5–1.5 mg/kg/d), several IV immunoglobulin infusions (400 mg/kg/d ×5 days), and immunosuppressive therapy, initially

From the Department of Brain and Behavioral Sciences (G. Cosentino, C.T.), University of Pavia; Clinical Neurophysiology Unit (G. Cosentino, E.A.), IRCCS Mondino Foundation, Pavia; Neurophysiopathology Department (M.R.), Villa Sofia-Cervello Hospital; Division of Pulmonology (DIBIMIS) (M.A.), Department of Internal Medicine, Villa Sofia-Cervello Hospital, Palermo; Department of Biomedicine Neuroscience and Advanced Diagnostics (F.B.), University of Palermo; Neurorehabilitation Unit (C.T.), IRCCS Mondino Foundation, Pavia; and Institute for Biomedical Research and Innovation (G. Crescimanno), Italian National Research Council, Palermo; Centre for Respiratory Complications of Neuromuscular Rare Disease (G. Crescimanno), Villa Sofia-Cervello Hospital, Palermo, Italy.

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Table Past or concurrent autoimmune comorbidities experienced by the patient

Autoimmune disease	Notes
Idiopathic/immune thrombocytopenic purpura	Onset in childhood, with spontaneous remission.
Antiphospholipid syndrome with high anticardiolipin IgG (ACA) titres	Concurrent disease responsible for recurrent venous thrombosis episodes in the lower limbs, treated with warfarin.
Undifferentiated connective tissue disease	Concurrent disease. Positive antinuclear antigen, ANA (1:160). Capillaroscopy showing microvascular abnormalities.
Myasthenia gravis	Diagnosed about 20 years ago based on clinical symptoms (muscle weakness with fatigue, fluctuating diplopia, and ptosis), presence of antiacetylcholine receptor (AChR) antibody and electrophysiologic abnormalities (single fiber EMG). At present considered in remission based on clinical symptoms, negative AChR antibody testing, and normal electrophysiologic assessment (single fiber EMG and repetitive nerve stimulation) on 2 different occasions. Multiple chest CT scans were negative for thymic abnormalities.
Insulin-dependent diabetes mellitus	Concurrent disease.

with azathioprine (up to 3 mg/kg/d) and subsequently with cyclosporine A (up to 4 mg/kg/d). Lately, rituximab (375 mg/m^2 IV for 4 doses) was added to the corticosteroid treatment, which induced a complete depletion of CD20$^+$ B-Cells, but no clinical improvement. Oral diazepam (10–15 mg/d) and baclofen (75 mg/d) were used to control muscle spasms, with partial benefit. Diazepam doses were not increased beyond 15 mg because of side effects, including daytime sleepiness and forgetfulness. Over the previous 2 years, respiratory crises occurred with increasing frequency (up to 2 per week) and severity of dyspnea, thus becoming a major concern that often required prompt sanitary interventions and multiple accesses to the emergency department. In many cases, dyspnea crises could be interrupted only with IV administration of diazepam. In the attempt to find an effective alternative therapy for the acute management of respiratory crises, we hospitalized the patients for testing the efficacy and usability of midazolam (5 mg/1 mL concentration) via the nasal route.

Midazolam is a short-acting benzodiazepine (BZD), roughly 1.5–2 times more potent than diazepam. When administered intranasally, midazolam is rapidly absorbed and acts very quickly, with possible superiority over the IV route when considering the time needed to place an IV catheter.[5,6] Intranasal midazolam is both effective and well tolerated in the acute treatment of status epilepticus. This BDZ has been approved by the FDA for seizure clusters in May 2019. Recent studies have confirmed its safety profile and support the feasibility of intranasal administration as a potential alternative for the out-of-hospital treatment of seizure emergencies.[7] Video 1 shows a representative respiratory crisis observed during hospitalization. The crisis was almost immediately interrupted by the nasal administration of midazolam 2.5 mg (0.5 mL) into each nostril by means of a mucosal atomization device. Immediately after treatment, the patient experienced a mild feeling of drowsiness that resolved within 2 hours, but no other side effects. Systolic and diastolic blood pressure moderately decreased for a few hours after treatment, but the values remained within physiologic limits. The average oxygen saturation levels were maintained within the normal range.

After we assessed safety and efficacy of treatment in 4 different occasions in the hospital setting, we trained the patient's relatives to administer the drug at home. Until now, more than 20 respiratory crises have been effectively and safely treated, with a frequency of about one administration every 2 weeks.

In conclusion, based on our multiple observations in a single case, intranasal midazolam administration appears an easily applicable and rapidly effective alternative treatment for respiratory crises due to spasms of the axial muscles in SPS, especially when an IV route is not available.

Classification of evidence

This is a single observational study without control and provides Class IV evidence.

Study funding

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Disclosure

The authors have no conflicts of interest to declare as regards this study. Go to Neurology.org/NN for full disclosures.

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Appendix Authors

Name	Location	Contribution
Giuseppe Cosentino, MD, PhD	University of Pavia, Italy	Drafting/revising the manuscript; Study concept or design; Analysis or interpretation of data; Data acquisition

Appendix *(continued)*

Name	Location	Contribution
Marcello Romano, MD	Villa Sofia-Cervello Hospital, Palermo, Italy	Drafting/revising the manuscript; Study concept or design; Analysis or interpretation of data; Data acquisition
Margherita Algeri, MD	Villa Sofia-Cervello Hospital, Palermo, Italy	Study concept or design; Data acquisition
Filippo Brighina, MD	University of Palermo, Italy	Drafting/revising the manuscript
Enrico Alfonsi, MD	IRCCS Mondino Foundation, Pavia, Italy	Drafting/revising the manuscript; Study Supervision
Cristina Tassorelli, MD, PhD	University of Pavia, Italy	Drafting/revising the manuscript; Obtaining Funding

Appendix *(continued)*

Name	Location	Contribution
Grazia Crescimanno, MD	Institute for Biomedical Research and Innovation, Palermo, Italy	Study concept or design; Data acquisition

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