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

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Neurol Neuroimmunol Neuroinflamm 2020;7:e715. doi:10.1212/NXI.0000000000000715

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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, and life-threatening respiratory crises have been occasionally reported and suspected to be responsible for sudden death in these patients. 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.

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, 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 (SpO2 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...
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
No targeted funding reported.

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

### Publication history
Received by Neurology: Neuroimmunology & Neuroinflammation January 20, 2020. Accepted in final form March 3, 2020.

### 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 |
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### 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                        |
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*Neurol Neuroimmunol Neuroinflamm* 2020;7;
DOI 10.1212/NXI.0000000000000715

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