

Stellate Ganglion Block Successfully Treats Long COVID/PASC: A Case Series

Luke D Liu MD

Neuroversion Inc.

Deborah L Duricka PhD (✉ dduricka@neuroversion.net)

Neuroversion Inc. <https://orcid.org/0000-0002-5057-6361>

Case Report

Keywords: COVID, PASC, Long-haul, Long COVID, stellate ganglion, sympathetic nervous system, dysautonomia, brain fog, SGB

Posted Date: September 10th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-873830/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

The SARS-CoV-2 pandemic has resulted in a secondary pandemic of individuals suffering from pernicious symptoms termed “Long COVID” or PASC. In spite of significant societal impact, the condition remains mysterious and effective treatment remains elusive. Individuals experience debilitating symptoms including fatigue, “brain fog,” loss or altered smell and/or taste, anxiety and depression. Most of these symptoms are included in the “sickness behavior response” initiated from the brainstem when levels of circulating pro-inflammatory cytokines are high. Ordinarily a feedback loop prevents excessive production of these cytokines, however the SARS-CoV-2 virus has demonstrated the ability to induce the sympathetic nervous system (SNS), likely due to imbalance between ACE1 and ACE2 activity. Persistent sympathetic drive causes increased cytokine release, which interferes with the feedback loop that ends “sickness behaviors.” The stellate ganglion is a paravertebral collection of sympathetic nerves located in the cervical region that provides a convenient entry point to reduce activity of the SNS using local anesthetic blockade. The stellate ganglion block (SGB) has a well-established safety and efficacy profile for a variety of conditions involving the SNS. In this case report series, we treated three consecutive “Long COVID” patients with SGB. All three patients reported significant and durable improvement in symptoms including fatigue, “brain fog,” and smell and taste derangements. Our findings provide evidence implicating dysautonomia as the main etiology of Long COVID/PASC symptoms and suggest that SGB is an effective intervention for this condition with the potential to change the course of the second COVID pandemic, “Long COVID”/PASC.

Summary

After recovering from SARS-CoV-2 infection, a number of individuals develop “Long COVID”/PASC. Symptoms include fatigue, “brain fog,” anosmia, and ageusia/dysgeusia. These symptoms overlap with “sickness behavior,” an expected autonomic nervous system (ANS) response to pro-inflammatory cytokines. COVID-19 induces this response, which may be perpetuated as dysautonomia in patients with Long COVID/PASC. Injection of local anesthetic onto the stellate ganglion, a cervical paravertebral collection of sympathetic nerves, reduces sympathetic output of the ANS. In this case series, we successfully treated three consecutive Long-haul COVID patients using SGB, implicating dysautonomia as the main etiology of Long COVID/PASC and suggesting a novel treatment.

Introduction

The global pandemic caused by the SARS-CoV-2 virus has resulted in millions of deaths and untold suffering worldwide. A subset of individuals develops a range of symptoms that persist indefinitely after recovery from acute infection. The constellation of symptoms, which can range from mild to debilitating, is known colloquially as “Long COVID” and formally as PASC (Post-Acute COVID-19 syndrome, or Post-Acute Sequelae of SARS-CoV-2 infection). Symptoms can include fatigue, shortness of breath, “brain fog,” sleep disorders, fevers, gastrointestinal symptoms, anosmia, dysgeusia, anxiety, and depression.

PASC can follow severe COVID-19 or develop following asymptomatic infection. The condition continues to baffle the medical community and effective treatments remain elusive.

The stellate ganglion is a collection of sympathetic nerves located paravertebrally between C6 and C7, with projections to the arm, head, and chest. The stellate ganglion block (SGB) was first described in the 1930s as a treatment for reflex sympathetic dystrophy of the upper limbs [1]. The stellate ganglion influences blood flow to the upper extremities, making blockade useful in the treatment of Raynaud's phenomenon and hyperhidrosis [2]. More recently, SGB is showing promise in the treatment of PTSD [3] [4], cardiac arrhythmia [5], hot flashes associated with cancer treatment and menopause [6], as well as immunological disorders such as allergies, asthma, atopic dermatitis, and ulcerative colitis [7]. Although the functional connectivity of the stellate ganglion in humans remains only partially known, central effects of SGB are hypothesized to occur due to communication with CNS structures that influence the sympathetic branch of the autonomic nervous system [7]. SARS-CoV2 has demonstrated the ability to cause post-acute sympathetically-mediated autonomic dysfunction affecting sleep [8], resting heart rate [9], orthostatic intolerance and dyspnea [10]. This case series provides evidence implicating dysautonomia as the main etiology of Long COVID/PASC symptoms and suggests that SGB is an effective intervention for this condition, with the potential to change the course of the second COVID pandemic, Long COVID/PASC.

Case Presentation

1. A 48-year-old male who recovered from severe COVID-19 presented to our clinic 16 months after onset of initial illness. The patient sustained significant lung damage during acute phase of infection and had required supplemental oxygen for more than a year. Due to deconditioning, he completed six months of physical therapy in order to resume activities of daily living. While he had intermittently regained some ability to detect smell and taste, these senses were distorted and generally unpleasant. The patient reported severe mental fogging and deficits including difficulty retrieving words, recalling numbers, difficulty recognizing familiar faces, and episodes of topographical disorientation in familiar places.

We performed right-sided SGB and observed the expected physiological responses (e.g., Horner's syndrome). Within hours, the patient reported reduction in mental fogging and partial restoration of taste. The following day, left-sided stellate ganglion block was performed. The patient reported additional improvement in his mental clarity and sense of taste. On follow-up at 11 days after his second SGB, the patient noted "incredible" durable improvement in his mental clarity and concentration, specifically citing restoration of numerical recall ability, word-finding capacity, and facial recognition. He had experienced no episodes of disorientation since treatment, and reported normal ability to smell and taste.

2. A 42-year-old female who recovered from a mild course of COVID mainly presenting as low oxygen saturation, fatigue, anosmia and dysgeusia, presented to our clinic eight months after onset of initial illness. Since recovering from acute illness, she continued to experience debilitating fatigue, mental fogging, difficulty concentrating, elevated resting heart rate, sleep disturbance, lack of appetite and

food aversion due to diminished and altered sense of taste and smell. Due to decrement in performance, she had been let go from her job and was teaching 4-hour CPR courses with difficulty, relying on her teaching manual to recall facts and procedures previously well known to her. The unpalatability of any food had led to a 30-pound weight loss that was continuing to progress. Patient charts indicated a resting HR in the 60s prior to COVID-19; at presentation she reports that it had not been less than mid-80s since recovering from acute COVID-19.

We performed right-sided SGB. The patient noted immediate improvement in her dysgeusia and marked improvement in mental clarity and concentration. She later recalled being able to drive home without conscious effort to recall the route, demonstrating noticeable improvement in procedural memory. Two days later we performed left-sided SGB. On follow-up at 22 days after her second SGB, the patient reported that her sleep had returned to normal and she felt rested upon awakening. Her resting HR was measured at 69, and she reported restoration of taste and smell. Since her treatment, she was able to teach a 9-hour course for CPR instructors without the need to reference the teacher's manual or written notes, demonstrating a drastic improvement in declarative memory. These improvements in symptoms were durable at 30-day follow-up.

3. A 44-year-old female contracted COVID-19 approximately eight months prior to her presentation for treatment of PASC. Her initial COVID-19 symptoms were loss of smell and taste, mental foginess, headache, and dyspnea. Approximately one week after onset of symptoms her headache worsened, prompting evaluation in the ER but not hospitalization. Her headache symptoms dissipated over the following two weeks, but she experienced declining cognitive function and developed stuttering speech, significant cognitive impairment, and hemi-sided paralysis, prompting hospitalization and evaluation for MCV. Her MRI demonstrated inflammation, but neither stroke nor viral encephalitis. She was discharged with a diagnosis of brain injury secondary to COVID-19 and prescribed intense occupational, physical, and speech therapy for profound deficits in procedural and declarative memory, speech impediment, impaired coordination, inability to concentrate, and debilitating fatigue. She was unable to continue her work as a special education teacher.

She presented to the clinic after approximately seven months of slow but steady improvement in her physical and mental condition with the help of intense daily physical, occupational, and speech therapy. She continued to experience debilitating fatigue and speech impediment, and had returned to limited duties and shortened hours at work. She reported that ongoing dysgeusia had led to food aversion and significant unintentional weight loss. She was experiencing generalized body pain (4/10) described as dull with pins and needles. When exacerbated, her pain reached 10/10 and she was unable to get out of bed. She noted that acute stress exacerbated her right-sided motor deficits. She also experienced intermittent headaches described as "crawling pain in my brain."

We performed right-sided SGB followed by left-sided SGB the following day. Within hours of the first procedure, the patient reported drastic improvement in smell and taste. At three-day follow-up she indicated that her physical and mental stamina had improved significantly, allowing her to perform

routine household activities without debilitating lapses in procedural memory. She began a new job as a high-school teacher and was able to teach a full day of classes, which she states would have been “impossible” prior to treatment. On follow-up at 15 days, the patient reported durable resolution of stuttering and 75% improvement in all other symptoms.

Discussion

A number of groups have noted the association between autonomic nervous system dysfunction and the symptoms of PASC [10] as well as the comorbidities associated with increased morbidity/mortality in COVID-19 [11]. The autonomic nervous system and immune system are inherently linked through the cholinergic anti-inflammatory pathway (CAP), a component of the parasympathetic nervous system in which the afferent vagus nerve senses pro-inflammatory cytokines and the efferent vagus nerve releases acetylcholine that binds the $\alpha 7$ subunit of the acetylcholine receptor (AChR) in macrophages, thereby inhibiting cytokine release [12]. This feedback loop prevents cytokine-associated tissue damage. In addition to its role in CAP, the afferent vagus nerve monitors cytokines and catecholamines in the periphery and reports levels to the brainstem where the information is integrated into complex behaviors. When circulating levels of pro-inflammatory cytokines and catecholamines are sufficient, the brain initiates “sickness behavior”—a constellation of autonomic responses including behavioral inhibition, fatigue, malaise, depressed mood, reduced social exploration, hyperalgesia, anhedonia, anxiety, and neurocognitive issues [13].

The targeting of the ACE2 receptor by SARS-CoV-2 has been speculated to cause an ACE1:ACE2 imbalance that leads to an excess of angiotensin II [14, 15], which activates sympathetic outflow to peripheral target organs including the heart and kidneys, an effect that is consistently seen in chronic heart failure (CHF) [16]. Circulating levels of norepinephrine (NE) in cardiac sympathoexcitation are increased due to spillover of 10–20% of synaptic NE into circulation [16]. While NE is largely associated with anti-inflammatory activity due to post-ganglionic activation of $\beta 2$ -adrenergic receptors in lymphoid tissues [17], circulating NE is also sensed by myeloid cells via $\alpha 1$ adrenoreceptors, leading to increased myeloid expression of cytokines and activating sickness behavior. In some cases, spillover NE may be sufficient to disrupt the CAP’s anti-inflammatory signal to macrophages and complete the feedforward loop seen in cytokine release syndrome [18], a condition that resembles the respiratory distress and multi-organ failure seen in severe COVID-19. We hypothesize that the chronic autonomic dysregulation known to follow SARS-CoV-2 infection [8–10] perpetuates sickness behavior after resolution of infection, leading to the symptoms seen in Long COVID/PASC. Reduction of sympathetic activation would be expected to break this vicious cycle of autonomic dysregulation.

Our patients uniformly reported significant improvement in fatigue, mental foggy, and memory issues after SGB, confirming a sympathetically mediated process involved in the maintenance of PASC symptoms. Given the involvement of the sympathetic nervous system in the initiation and maintenance of sickness behavior, we believe that SGB produces these beneficial effects by attenuating chronically

aberrant sympathetic dominance. This supports the theory that dysautonomia is the main etiology of Long COVID/PASC.

The olfactory and gustatory improvement immediately following SGB is as inexplicable as the deterioration of these senses with SARS-CoV-2 infection, but presumably involves a sympathetically mediated process. Numerous drugs from multiple classes are associated with changes in smell and taste, including the ACE2 inhibitor losartan [19] and the sympathomimetic midodrine [20]. Improvement in anosmia after SGB has been reported previously, although the mechanism for the effect is unknown [21–23].

The stellate ganglion block has been used for nearly a century to treat a variety of sympathetically mediated medical conditions and its safety profile has been well established. Its application in treating Long COVID/PASC is novel. The lack of effective treatments for Long COVID/PASC makes the stellate ganglion block an attractive therapeutic modality that deserves further investigation.

Declarations

ACKNOWLEDGEMENTS

The authors gratefully acknowledge Eugene Lipov MD for illuminating conversations about SGB and the autonomic nervous system, as well as spearheading the exploration of utilizing cervical sympathetic blocks for conditions related to dysautonomia.

CONFLICT OF INTEREST STATEMENT

Luke D Liu MD is the Medical Director and owner of Neuroversion Inc., an interventional pain management practice in Anchorage Alaska that provides stellate ganglion block, among other treatments. Deborah L Duricka PhD is employed by Neuroversion Inc. No other conflicts exist.

DECLARATION OF CONSENT

Each patient consented to treatment per normal protocol, and additionally consented to use of their de-identified case information for publication. Both consent statements are recorded in their Electronic Health Records.

References

1. White, James C. Diagnostic Novocain block of the sensory and sympathetic nerves: A method of estimating the results which can be obtained by their permanent interruption. *The American Journal of Surgery*, vol. 9, no. 2, pp. 264–277, August 1930.
2. Rickles, Julian A. Ambulatory Use of Sympathetic Nerve Blocks: Present Day Clinical Indications. *Angiology*, vol. 28, no. 6, pp. 394–402, June 1977.

3. Eugene G. Lipov MD, Maryam Navaie DrPH, Eric T. Stedje-Larsen MC USN, et al. A Novel Application of Stellate Ganglion Block: Preliminary Observations for the Treatment of Post-Traumatic Stress Disorder. *Military Medicine*, vol. 177, no. 2, p. 125–127, February 2012.
4. Sean W Mulvaney, James H Lynch, Matthew J Hickey, et al. Stellate Ganglion Block Used to Treat Symptoms Associated With Combat-Related Post-Traumatic Stress Disorder: A Case Series of 166 Patients. *Military Medicine*, vol. 179, no. 10, p. 1133–1140, October 2014.
5. Ying Tian, Erica D Wittwer, Suraj Kapa, et al. Effective Use of Percutaneous Stellate Ganglion Blockade in Patients With Electrical Storm. *Circulation: Arrhythmia and Electrophysiology*, vol. 12, no. 9, p. e007118, September 2019.
6. Eugene Lipov, Briana Marie Kelzenberg. Stellate ganglion block (SGB) to treat perimenopausal hot flashes: clinical evidence and neurobiology. *Maturitas*, vol. 69, no. 2, pp. 95–96, June 2011.
7. Eugene Lipov, Vicko Gluncic, Ivan K. Lukić, Kenneth Candido. How does stellate ganglion block alleviate immunologically-linked disorders? *Medical Hypotheses*, vol. 144, November 2020.
8. Giorgio Quer, Jennifer M Radin, Matteo Gadaleta, et al. Wearable sensor data and self-reported symptoms for COVID-19 detection. *Nature Medicine*, vol. 27, no. 1, pp. 73–77, January 2021.
9. Jennifer M Radin, Giorgio Quer, Edward Ramos, et al. Assessment of Prolonged Physiological and Behavioral Changes Associated With COVID-19 Infection. *JAMA Network Open*, vol. 4, no. 7, 7 July 2021.
10. Melanie Dani, Andreas Dirksen, Patricia Taraborrelli, et al. Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies. *Clinical Medicine*, vol. 21, pp. e63-e67, 26 November 2021.
11. Andrea Porzionato, Aron Emmi, Silvia Barbon, et al. Sympathetic activation: a potential link between comorbidities and COVID-19. *The FEBS Journal*, vol. 287, no. 17, pp. 3681–3688, September 2020.
12. Tracey, Kevin J. Physiology and immunology of the cholinergic antiinflammatory pathway. *The Journal of Clinical Investigation*, vol. 117, no. 2, pp. 289–296, February 2007..
13. Robert Dantzer, Jason C O'Connor, Gregory G Freund, Rodney W Johnson, Keith W Kelley. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature Reviews Neuroscience*, vol. 9, no. 1, pp. 46–56, January 2008.
14. Krishna Sriram, Paul A. Insel. A hypothesis for pathobiology and treatment of COVID-19: The centrality of ACE1/ACE2 imbalance. *British Journal of Pharmacology*, vol. 177, no. 21, pp. 4825–4844, 24 April 2020.
15. Pasquale Pagliaro, Claudia Penna. ACE/ACE2 Ratio: A Key Also in 2019 Coronavirus Disease (Covid-19)? *Frontiers in Medicine*, vol. 7, no. 335, 18 June 2020.
16. Borovac JA, D'Amario D, Bozic J, et al. Sympathetic nervous system activation and heart failure: Current state of evidence and the pathophysiology in the light of novel biomarkers. *World J Cardiol*. 2020 Aug 26;12(8):373–408.
17. Drashya Sharma, J. David Farrar. Adrenergic regulation of immune cell function and inflammation. *Seminars in Immunopathology*, vol. 42, p. 709–717, 20 November 2020.

18. Verena Staedtke, Ren-Yuan Bai, Kibem Kim, et al. Disruption of a self-amplifying catecholamine loop reduces cytokine release syndrome. *Nature*, vol. 564, p. 273–277, 12 December 2018.
19. R G Schlienger, M Saxer, W E Haefeli. Reversible ageusia associated with losartan. *Lancet*, vol. 347, no. 8999, pp. 471–472, 17 February 1996.
20. Tim M Young, Christopher J Mathias. Taste and Smell Disturbance with the Alpha-Adrenoceptor Agonist Midodrine. *Annals of Pharmacotherapy*, vol. 38, pp. 1868–1870, December 2004.
21. Moon HS, Lee HJ, Sung CH, Lim SJ, Choi JH. The Efficacy of Stellate Ganglion Block in Sensorineural Anosmia Patients Unresponsive to Steroid Therapy. *The Korean Journal of Pain*, vol. 20, no. 2, pp. 154–157, December 2007.
22. Hyun-Joo Park, Dong Yeon Kim, Jung-Ho Bae, Seung-Sin Lee. The Effect of Stellate Ganglion Block on the Treatment of Sensorineural Olfactory Disorder Following Upper Respiratory Tract Infection. *Korean Journal of Otorhinolaryngology*, vol. 56, pp. 84–89, January 2013.
23. Ho Sik Moon MD, Jin Young Chon MD, Sang Hoon Lee MD, Yu Mi Ju MD, and Choon Ho Sung MD. Long-term Results of Stellate Ganglion Block in Patients with Olfactory Dysfunction. *Korean Journal of Pain*, vol. 26, no. 1, pp. 57–61, 31 January 2013.