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Severe Stiff-Person Syndrome After COVID: The First Video-Documented COVID Exacerbation and Viral Implications

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Abstract

Objectives

To describe a patient with mild GAD-positive stiff-leg syndrome (SLS) who developed severely disabling stiff-person syndrome (SPS) 1 week after mild COVID-19 and discuss the impact of viral implications.

Methods

Video-documented serial clinical observations at baseline, after acute COVID-19, and after IVIG treatments.

Results

A 39-year-old man with left-SLS was stable during a 2-year follow-up with low-dose antispasmodics, working fully and functioning normally, even able to run. One week after mild COVID-19, he started to experience generalized SPS symptomatology that steadily worsened the following 2–3 weeks, becoming unable to walk, requiring a walker, with significant thoracolumbar and bilateral leg stiffness and spasms. GAD ab were very high. After 3 monthly IVIg infusions he showed improvements, but his gait remains significantly stiff. All clinical changes, from baseline to post-Covid, and then post- IVIg have been video-documented.

Discussion

This is the first, clearly documented, severe GAD-positive SPS after COVID-19. Although viral or postviral causation can be incidental, the temporal connection with acute COVID-19, the severe disease worsening after symptom-onset, and the subsequent steady improvement after IVIg, suggest viral-triggered autoimmunity. Because COVID-19 reportedly can trigger or worsen GAD-associated diabetes type 1 through proinflammatory mediators, and SPS has been reportedly triggered by West Nile Virus, possibly through molecular mimicry, this case of acutely converting GAD-SLS to GAD-SPS suggest the need to explore viral etiologies in patients with GAD-SPS experiencing acute, long-lasting episodic exacerbations of stiffness and spasms.

MORE ONLINE

Video

Introduction

Stiff-person syndrome (SPS) is characterized by stiffness in the limb and axial muscles, episodic painful muscle spasms often triggered by anxiety and task-specific phobias, and startle responses resulting in stiff and spastic gait and uncontrolled falls steadily leading to disability.[1-3] SPS is due to autoimmune neuronal hyperexcitability connected to impaired reciprocal GABAergic inhibition associated with very high GAD-65 antibody titers in the serum and CSF.[1] Except in cases of paraneoplastic association, it is unknown what triggers SPS, especially the sudden onset of long-lasting spasms. Although viruses have been implicated as triggers in various autoimmune diseases, there is no evidence that they have a role in SPS either as disease triggers

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or as inducers of severe postviral exacerbation, except of 1 case associated with West Nile Virus (WNV) infection.[4] Although up to 35% of patients with SPS have GAD-positive diabetes mellitus type 1 (DM1),[1,5] and some cases with DM1 are reportedly triggered or worsened by enteroviruses and COVID-19,[6,7] there is no evidence that these viruses can also acutely trigger or worsen SPS. This is especially relevant because COVID-19 has been implicated in triggering several neuronal autoimmunities.[8-10]

We now describe the first case of a patient with very mild GAD-positive stiff-leg syndrome (SLS) with disease limited to the left leg who was fully functioning for years, but 1 week after COVID-19 started to worsen and over 3 weeks developed severe full-blown SPS becoming acutely disabled due to generalized—video-documented—severe stiffness and spasms. Because his newly developed SPS has been steadily improving with IVIg, the case suggests an enhanced viral-triggered GAD antibody–associated autoimmunity.

Clinical Presentation

During 2018, a 39-year-old man insidiously developed muscle spasms in the left leg, difficulty walking, falls, and sensitivity to unexpected noises. He had elevated GAD antibodies in the spinal fluid and was diagnosed with SPS. He was healthy other than Hashimoto thyroiditis. He was treated with low-dose clonazepam, 2 mg/d, and improved. IVIg, 2 g/kg monthly for 2 months, and baclofen did not significantly help. Patient was referred to our department, being followed up by us for the past 2 years. When examined, he had minimal stiffness limited to the left leg and left lumbosacral paraspinal with left knee "hung-up" reflex, consistent with SLS; his mild stiffness improved further with gabapentin (300 mg TID). His serum GAD65 ab titers were 50 times above normal (>250; normal 0–5 IU/mL). The patient is working full time without limitations, traveling throughout the country and abroad, giving live lectures, as required by his job, without experiencing triggered spasms. When last seen on April 13, 2023, he was stable with only slightly increased stiffness in the left lower extremity and back, fully functioning, being even able to run (Video 1).

On April 27, 2023, 2 weeks after his last clinic visit, he got a mild case of COVID, confirmed with rapid home test, with fever and congestion not requiring anti–COVID treatment, but a few days afterward, while he became afebrile, he started to experience generalized stiffness and spasms. Symptoms rapidly progressed the following 2–3 weeks, while COVID negative, to the point of becoming unable to walk due to painful stiffness in both lower extremities and painful spasms in the thoracolumbar and cervical paraspinal muscles that have been awakening him up in the middle of the night. The patient has been vaccinated and boosted and states that he also had COVID in May 2021 but without any neurologic sequalae. When seen 2 weeks later, on May 22, 2023, he was unable to ambulate without support, exhibiting sudden—without startle reflex—severe muscle spasms in the legs and paraspinal muscles. He could only take a few steps with support and started using his daughter's stroller as a walker (Video 2); his wife was helping him to get up and assisting him in routine daily activities. GAD ab titers were again high, 50 times > normal. Patient was started on IVIg, though he was reluctant, because IVIg did not help him when tried 3 years ago. After 1 month he started to improve, not requiring support when walking around the house, but continued to need the baby stroller as a walker when outside because a single cane was not supportive enough to allow secure ambulation without falling. After the third IVIg infusion, he improved much more but still not in his pre-COVID status; he is now ambulating more freely but has difficulty when crossing the street or "walking fast" (Video 3). Because he is improving every month, he continues receiving monthly IVIg.

Discussion

This is the first post–COVID-associated severe SPS. Although observational and fully aware that an association is not necessarily a causation, the acute onset of such severe worsening 1 week after COVID with conversion from mild and physically independent SLS status to generalized SPS with severe disability requiring a walker, strongly suggests a virus-triggered SPS autoimmunity or postviral inflammatory process. His ongoing response to IVIg further supports a COVID-triggered immune imbalance.

COVID-19 can trigger systemic neuroautoimmunities[8-10] but this is the first case of SPS. Within the SPS spectrum disorders, a case of PERM with glycine receptor antibodies has been recently reported during the acute COVID infection[11]; PERM has been, however, also reported with EBV, hepatitis C, and brucellosis,[11,12] but in all cases, the temporal window between the infection and symptom onset was either long or unspecified. The most compelling support of an association between COVID-19 and GAD autoimmunity relates to DM1 based on several reports that COVID-19 infection can trigger or severely worsen DM1 with GAD antibodies directed against conformational GAD epitopes due to augmented proinflammatory cytokines and recruitment of $CD8^+$ T cells.[6,7] Such an association—even if GAD ab are not pathogenic—is of direct relevance to SPS because 35% of patients with SPS have DM1 with GAD ab directed against linear epitopes.[1,5] Whether the worsening of DM1 after COVID-19 also triggers mild but unrecognized SPS symptomatology, possibly by converting the conformational DM1-associated GAD65 epitopes to linear ones connected with SPS,[1,5] remains unknown. This possibility would be viable if there is amino acid sequence homology between COVID-19 and GAD because such cross-reactivity and molecular mimicry can enhance a specific immune response that could also explain the present case of converting SLS to SPS; this possibility has been previously proposed in a case of SPS

manifested after WNV infection, based on partial amino acid sequence homology between GAD65 and WNV.[4]

This case is clearly a rare event, not seen among the large number of patients with SPS we follow-up during the pandemic; because SPS is also a rare disease, the frequency of COVID-19–related consequences, if any, in SPS spectrum disorders is difficult to assess. The main message of this case, considering the strong associations discussed earlier, is that viruses have the potential to enhance SPS autoimmunity either by triggering disease or worsening disease status. COVID-19 is known to upregulate immune responses leading to the production of various proinflammatory mediators, suppressing Tregs, and enhancing key cytokines, especially IL-6, which has been now associated with GAD antibody production in GAD spectrum disorders.[13] Although the precise time onset of autoimmunities following COVID-19 is variable, in well-documented post–COVID-19 autoimmune diseases, like Guillain-Barré syndrome,[9,14] this occurs immediately after the infection, as in this case, probably when Th1 responses are dysregulated with bystander activation of preexisting memory B cells.[15]

In summary, considering all the possibilities and limitations discussed earlier, this well-documented case of acute development of severe disabling SPS from a previously stable SLS highlights the potential to explore whether viral infections, by enhancing systemic autoimmunity or molecular mimicry, play a role in triggering some of the acute but long-lasting periods of severe spasms and stiffness, frequently seen in patients with SPS but remain unexplained.

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Name	Location	Contribution
Marinos C. Dalakas, MD	Department of Neurology, Thomas Jefferson University, Philadelphia, PA; Neuroimmunology Unit, National and Kapodistrian University of Athens Medical School, Athens, Greece	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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