

CASE REPORT

A case of dysautonomia after COVID-19 infection in a patient with poorly controlled type I diabetes

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Abstract

COVID-19 has been linked to dysautonomia in the current literature, as has uncontrolled diabetes. Here, we present a case report of severe dysautonomia following a COVID-19 infection in a patient with pre-existing poorly controlled type-1 diabetes. This patient exhibited symptoms consistent with both postural orthostatic tachycardia syndrome (POTS), as well as orthostatic hypotension. His symptoms became so severe that he was unable to come to a standing position without experiencing syncope. Extensive workup was completed to identify an alternative cause of his dysautonomia with inconclusive results. Dysautonomia can have devastating consequences in regard to physical, social, and psychological health. Counseling individuals with poorly controlled diabetes about the importance of maintaining tight blood glucose control and avoiding COVID-19 infection should be primary interventions when treating patients with this DM1. Early detection and management of diabetes mellitus, COVID-19, and of possible resultant dysautonomia through medical interventions, as well as lifestyle changes, are extremely important measures to avoid development of dangerous and potentially life-threatening consequences.

KEYWORDS

COVID-19, dysautonomia, orthostatic hypotension, postural orthostatic tachycardia syndrome, type I diabetes

1 | INTRODUCTION

Many studies suggest a link between dysautonomia and COVID-19 infection. Dysautonomia is a term that refers to improper functioning of sympathetic or parasympathetic nervous systems which include, but are not limited to, symptoms such as labile blood pressures, orthostatic hypotension, impotence, bladder dysfunction, and alterations in bowel functions.^{1,2} Notably, COVID-19 has been linked to orthostatic intolerance syndromes including either postural hypotension or tachycardia.³ Orthostatic

hypotension is defined as a decrease in blood pressure of >20 mmHg systolic and >10 mmHg diastolic after postural changes such as supine to sitting and/or sitting to standing position.⁴ Postural orthostatic tachycardia syndrome (POTS) is defined as orthostatic symptoms in the absence of hypotension with an increase in heart rate of 30 bpm or more when standing for more than 30 s or 40 bpm in those age 12–19.⁵ It is presumed that these symptoms may be related to immune-mediated disruption of the autonomic nervous system resulting in long-term orthostatic intolerance syndromes.³

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Furthermore, dysautonomia is a well-documented finding in diabetic patients with neuropathy. Dysautonomia can manifest as symptoms similar to those that are precipitated by COVID-19 including increased resting heart rate, impaired exercise tolerance and decreased baroreflex sensitivity with abnormal blood pressure regulation and orthostatic hypotension.⁶ It is conceivable that patients with increased risk for dysautonomia due to an underlying condition, such as Type 1 diabetes, are more likely to suffer from dysautonomia secondary to an infection such as COVID-19. The goal of this case report is to discuss dysautonomia in the setting of acute COVID-19 infection in addition to long-standing poorly controlled diabetes.

2 | CASE PRESENTATION

A 20-year-old man with past medical history significant only for poorly controlled Type 1 diabetes mellitus (DM1), peripheral neuropathy, and previous admission/treatment of diabetic ketoacidosis presented to the ED for evaluation of chest pain and syncope. Chest pain was accompanied by sensation of dyspnea, lightheadedness, and sensation of racing heart rate. Symptoms were notably described when patient attempted to arise from supine position and worsened with exertion. The patient also described multiple syncopal episodes following onset of these symptoms, described by family as brief periods of unconsciousness lasting roughly 2–5 min after each syncopal event.

Home medications included only subcutaneous insulin, which the patient admitted to taking most of the time with occasional missed doses. His family history was noncontributory. Of note, the patient was admitted to the hospital on several previous occasions, for DKA treatment in addition to presentation with similar symptoms noted in this case report. DKA is generally defined as a blood glucose greater than 250 mg/dl with acidosis, ketonemia/ketonuria, and a high anion gap.

Vitals signs on initial admission were as follows: blood pressure was 102/69 mmHg; pulse was 94 bpm; respirations were 17 rpm; he was saturating 99% on room air.

Physical examination was notable for orthostatic blood pressures with an increase in heart rate from 100 to 140s upon postural change from sitting to standing. Prior to the current episode, the patient had six hospital admissions for similar symptoms starting roughly 3 months prior to the current episode. Interestingly, patient reportedly tested positive for COVID-19 at an outside facility just prior to the initial onset of the described symptoms, but all COVID tests performed as inpatient returned negative. Given his history of poorly controlled Type 1 diabetes and findings of DKA with severe glucosuria and frequent urination, his initial hospital visits were attributed orthostatic

hypotension and chest pain secondary to significant dehydration. Workup for acute coronary syndrome (ACS) and pulmonary embolism (PE) were conducted during each previous hospital evaluation, with negative results for acute underlying cardiac conditions.

Blood glucose on admission was 315 mg/dl without an anion gap. Blood glucose was managed inpatient with basal bolus insulin titrated as necessary to maintain 100–200 mg/dl. This ranged from 50 to 70 mg Lantus QHS and 7 to 20 mg Glargine three times daily with meals. Of note, syncopal episodes while inpatient were not related to hypoglycemic episodes or to administration of insulin. The patient's blood glucose never fell below 115 mg/dl while inpatient. Syncopal episodes only occurred when the patient was upright, usually when ambulating to the restroom. These did not coincide with drastic changes in blood sugars. In addition, sodium and potassium levels were within normal limits for the duration of the patient's hospital stay.

Transthoracic echocardiogram (TTE) was performed, results significant for left ventricular ejection fraction (LVEF) of 35% and aortic root dilatation concerning for COVID myocarditis. However, subsequent TEEs revealed LVEF of 40% with a normal aortic root and cardiac MRI showed LVEF of 52%. TEE generally offers superior visualization of posterior cardiac structures, and therefore, these results were used to rule out aortic root dilatation as the cause of the patient's symptomology.

Plasma metanephrines and aldosterone were tested and within normal limits. Cortisol level was checked as well, which was below normal limits. Subsequent ACTH and cosyntropin stimulation tests were normal.

On several instances postural tachycardia was *not* associated with orthostatic hypotension, which suggested possible POTS. Midodrine trial was attempted, unfortunately that medication was discontinued due to side effects of nausea and vomiting. The patient was started on fludrocortisone 0.05 mg once daily for 1 week with no improvements in symptomology.

Because of the patient's uncontrolled diabetes and peripheral neuropathy, diabetic autonomic dysfunction was considered. Ophthalmology was consulted for evaluation of diabetic eye disease; workup was completed with no evidence for diabetic retinopathy. An outpatient appointment was scheduled with neurology for further workup; however, the patient did not attend this appointment.

Diagnosis of Marfan was also considered on prior hospitalizations due to the patient's tall and lanky stature. However, he has no family history of Marfan syndrome, and his symptoms did not begin until after he tested positive for COVID-19. In addition, his aortic diameter Z score was 0.68 (criteria >2). He had no history of dissection or

acute sudden change in vision. The patient was negative for wrist and thumb signs, and he did not exhibit pectus excavatum.

FT4, TSH, prolactin, ferritin, folate, and B12 were all within normal limits. Heavy metals were tested and not detected in serum. All toxicology screenings were negative. In addition, ANA returned negative.

During his hospital stay, the patient was essentially bed-ridden, as he was unable to come to a standing position without feeling as though he was going to pass out. All initial treatment therapies failed to cure his symptoms. At discharge, he was instructed to monitor his glucose levels regularly and follow up outpatient with his endocrinologist. For his dysautonomia, he was instructed to optimize his oral fluid intake, use compression stockings, liberalize sodium intake, and enact any positional changes slowly to allow for body acclimation. Other follow-up appointments included neurology, cardiology, internal medicine, and eye clinic.

Following discharge, he was unable to return to work and opted to move in with family for support. A referral was placed for the patient to be seen at another facility. Workup from that facility has not yet been obtained.

3 | DISCUSSION

The mechanism by which COVID-19 causes dysautonomia is currently being explored, but several hypotheses exist including direct viral invasion of the CNS, as its small size allows the virus to penetrate the blood brain barrier (BBB), where the virus appears to damage neurons after viral binding to ACE2 receptors in the endothelium of the BBB.^{7,8} Alternatively, there could be an indirect effect of the cytokine storm on mitochondria or on other nerve fibers.⁹ Further studies will be necessary to identify exactly how COVID-19 causes autoimmune dysregulation; however, the underlying cause may be consistent with direct cellular damage.

Treatment for COVID-19-related dysautonomia will include lifestyle changes such as adequate sodium and fluid intake, compression stockings for improved peripheral blood flow, and graduated exercise programs to improve deconditioning that may also lead to postural tachycardia.¹ In severe cases of heart rate and blood pressure dysregulation, medications such as beta blockers, ivabradine, fludrocortisone, or midodrine may be used for symptomatic management.¹

Diabetic autonomic neuropathy, however, has been explored for several years in the literature. The prevalence of diabetic autonomic neuropathy varies significantly between studies due to the lack of a standard definition as well as the variable clinical manifestations in patients

with this disease.^{6,10} Clinical manifestations include exercise intolerance, cardiovascular lability, orthostatic hypotension, silent myocardial ischemia, and cardiac denervation syndrome.¹⁰ Many hypotheses exist for pathogenesis of the disease state, including metabolic insult to nerve fibers, neurovascular insufficiency, autoimmune damage, and neurohormonal growth factor deficiency.¹⁰ Research involving diabetic autonomic neuropathy is extremely important, because cardiac autonomic neuropathy is associated with sudden death due to asymptomatic ischemia causing lethal arrhythmias such as QT prolongation.¹⁰ Recent studies have suggested that diabetic cardiac autonomic neuropathy may not be an independent cause of death as coronary atherosclerosis is common in individuals with diabetes and may be a confounding variable in this study.¹¹ That being said, the current literature suggests that diabetic retinopathy is associated with autonomic dysfunction in patients with both type 1 and type 2 diabetes mellitus.¹² Our patient did not have evidence of diabetic retinopathy despite his extensive hyperglycemic history, which suggests an alternative cause for the dysautonomia.

It has been demonstrated that long-term poor glycaemic control increases the risk of developing advanced diabetic neuropathy.¹³ Studies have also shown that intense glycaemic control prevented abnormal heart rate variation and slowed deterioration of autonomic dysfunction for individuals with type 1 diabetes, specifically in regard to cardiovascular autonomic dysfunction.¹⁴ Treatment for these individuals includes managing hyperglycemia and emphasizing the importance of diet and exercise. Other treatment options include agents that slow the progression of end-organ damage, such as ACE inhibitors as well as those that control blood pressure and hypercholesterolemia.¹⁰ Symptomatic management for heart rate and blood pressure dysregulation can also be considered in severe cases with midodrine, clonidine, mineralocorticoids, or nonselective beta blockers.⁶

4 | CONCLUSION

Patients with poorly controlled diabetes who also become infected with COVID-19 appear to be at increased risk for autonomic dysfunction and can have devastating consequences in regard to physical, social, and psychological health. Counseling individuals with poorly controlled diabetes about the importance of maintaining tight blood glucose control and avoiding COVID-19 infection (i.e., vaccinations and boosters, use of face masks, proper hand hygiene, and avoidance of sick individuals) should be primary interventions when treating patients with this DM1. Early detection and management

of diabetes mellitus, COVID-19, and of possible, resultant dysautonomia through medical interventions as well as lifestyle changes are extremely important measures to avoid development of dangerous and potentially life-threatening consequences.

AUTHOR CONTRIBUTIONS

Lorry Elizabeth Aitkens: Conceptualization; data curation; investigation; visualization; writing – original draft; writing – review and editing. **George Downey:** Conceptualization; data curation; formal analysis; investigation; resources; supervision; visualization; writing – review and editing.

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CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

CONSENT

Written informed consent was obtained.

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