

An Association of Takotsubo Cardiomyopathy with Guillain-Barré Syndrome

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Background: The association between Guillain-Barré syndrome (GBS) and Takotsubo cardiomyopathy (TC) has been appreciated for over two decades, while the physiological mechanisms between the two conditions are less so. In the time since, the progress in understanding molecular mechanisms and the accumulation of reported cases in the literature together have provided the beginnings for a deeper understanding of the disease pathways connecting these two conditions.

Methods: Case report.

Results: We report a 75-year-old woman with a history of prior TC who presented with symmetric bilateral paresthesias and weakness all preceded by symptoms concerning for an upper respiratory infection. The patient required intubation shortly after arrival due to respiratory failure, and routine electrocardiogram found evidence of ST-elevation myocardial infarction in multiple leads. Subsequent echocardiogram revealed findings consistent with TC, and electromyographic evaluation confirmed GBS. The patient clinically improved with plasmapheresis and had returned to her cardiac and neurologic baselines on outpatient follow-up.

Conclusion: GBS contributes directly to the pathogenesis of TC, both through direct action on cardiac nerves and an increase in resting sympathetic tone. While the stress of intubation likely contributes to a sympathogenic state within GBS, it is unlikely the principal factor predicting the development of TC within this unique subset of patients. TC should be considered in any patient with an acute neuropathy whenever signs of progressive dysautonomia are present.

Keywords: Takotsubo cardiomyopathy, myocardial stunning, Guillain-Barré syndrome, dysautonomia

Plain Language Summary

Guillain-Barré Syndrome (GBS), a transient paralysis from autoimmune nerve damage, and Takotsubo Cardiomyopathy (TC), a temporary expansion and paralysis of part of the heart, both are regarded as rare conditions. Their co-occurrence, while rarer still, is common enough for a connection to be considered between the two. Included is an example case of a 75-year-old woman in which they occurred together following a mild upper respiratory illness. The most common reasoning for this connection is emotional stress, which tends to happen when a patient needs mechanical support to breathe. While this explanation may satisfy on an individual basis, it fails to explain larger trends: a TC would be expected in patients who need support breathing, such as the critical care population. After understanding the overlap between these conditions, the autonomic nervous system and the effects of its' dysfunction in this context must be considered. GBS is capable of directly disrupting the autonomic nervous system, with the resulting dysautonomia potentially severe enough to lead to the development of a TC. Elevated catecholamines, a common result of autonomic dysregulation, should be recognized not only as evidence of a potential underlying dysautonomia, but most importantly as a risk factor for the development of TC. This is especially relevant to the COVID-19 pandemic, where steroids are given to any patient needing more than minimal supplemental oxygen.

Introduction

Of the acute paralytic neuropathies Guillain-Barré Syndrome (GBS) is both the most common and most severe.¹ Among patients hospitalized with GBS approximately 11.3% and 3.8% experience disruption in pulmonary and cardiac function, respectively, while severe dysautonomia including arrhythmias and intense blood pressure fluctuations occur in 20%.

Cause of death varies, with unexplained cardiac arrest being among the most commonly reported.² While cardiac dysfunction in association with GBS is common, involvement to a degree of severity consistent with Takotsubo Cardiomyopathy (TC) has only been reported in isolated cases.

The term Takotsubo Cardiomyopathy was first used to describe the shape of an affected left ventricle in systole, which resembled the octopus-catching pot of Japanese origin from which the name was derived.³ Only recently, in 2018, was a worldwide consensus reached on the diagnostic criteria for TC.⁴ The classical apical ballooning pattern for which takotsubo was named arises in 81.7% of patients while the midventricular, basal, and focal forms occur in 14.6%, 2.2%, and 1.5% of patients, respectively. The subdivision of TC is based on the region of wall-motion abnormality present, each of which does not map onto any known vaso-occlusive syndrome distribution.⁵

Case Presentation

A 75-year-old female with a history significant for hypertension and stress cardiomyopathy initially presented to a community hospital after several days of progressive weakness accompanied by symmetric bilateral paresthesias in the distal extremities, all in the context of 10 days of cough, malaise, and headache. She was found to be severely thrombocytopenic with platelets resulting 22,000 and was subsequently transferred to our institution for consideration of plasmapheresis for suspected immune thrombocytopenia.

On arrival to our emergency department the patient experienced increasing respiratory weakness prompting intubation. ECG revealed new ST elevations in leads I, II, III, AvF, and V3-V6 concerning for STEMI in association with a troponin of 0.07. Bedside transthoracic echocardiogram (TTE) showed mid-distal left ventricular dysfunction with an estimated ejection fraction of 25–30%. Emergent cardiac catheterization found mild non-obstructive atherosclerotic burden inconsistent with the patient's echographic presentation; findings indicative of Takotsubo cardiomyopathy.

Following admission to the ward she was started on captopril 3.125mg TID and metoprolol 6.25mg TID, as well as dexamethasone 40mg qDay and IVIG 400mg/kg qDay for a total of 4 and 5 days respectively. On hospital day one she was noted to have 2/5 weakness in neck flexion and shoulder extension, with 4/5 strength in the distal arms bilaterally and in all lower extremity motions. Sensation to pinprick was not assessed, however sensation to light touch was intact, she was areflexic throughout, and plantar reflexes were upgoing bilaterally. Lumbar puncture yielded clear colorless fluid with an analysis somewhat atypical of that normally expected with GBS; elevations in both RBCs and WBCs, 7 and 38 respectively, along with an elevated glucose and normal protein. Electrophysiological testing found a diffuse neuropathic process with both demyelination and axonal loss; these findings in context with the patient's clinical deficits were consistent with Guillain-Barre Syndrome, pharyngeal-cervical-brachial variant.

Her neurologic exam worsened over the following two days reaching a nadir of 0/5 strength in neck flexion, and throughout the bilateral upper and proximal lower extremities; toe flexion was somewhat preserved to 3/5 bilaterally. Light touch was intact throughout, reflexes remained absent, and Babinski sign remained positive on both sides. Repeat TTE the following day demonstrated a structurally normal left ventricle with hyperdynamic function in the ventricular base and severe hypokinesis of the mid and apical segments. LVEF was estimated at 25%.

Repeat TTE performed on hospital day 10 showed continued apical hypokinesis, with interval improvement in the mid myocardial segments and an EF improved to 50%. Plasmapheresis was initiated as the patient's respiratory condition had not shown sufficient response to IVIG. Over the next 10 days the patient's captopril was held and she received treatment every other day for a total of 5 sessions. This was accompanied by progressive improvement in respiratory status with liberation from the ventilator on hospital day 12. On hospital day 16, the patient's motor exam had improved significantly with 4–5/5 strength in both upper and lower extremities. Follow-up with Neurology a month later found that the patient had almost completely returned to her neurologic baseline, and at 18 months follow-up she was asymptomatic.

Written informed consent was obtained from the patient for the publication of this case report and the information contained within.

Discussion

The emerging field of Neurocritical Care has contributed to understanding Takotsubo Cardiomyopathy's pathophysiology by appreciating the associations between TC and its' occurrence with multiple intracranial pathologies. Most notable is

subarachnoid hemorrhage, where 20% of patients with SAH were found to have clinically significant elevations in serum cardiac troponin.⁶ Acute stroke has also been linked to the development of TC, specifically lesions within the right dorsal anterior insular cortex, an essential autonomic regulator of cardiac function.⁷ The lack of severe neurological deficits in the presented patient reassured against a major intracranial event.

Direct catecholamine toxicity, myocardial stunning, and dysregulated vasoreactivity comprise the three distinct arms of TC's pathogenesis. Histological investigations found that this "catecholamine toxicity" frequently occurs in the setting of cardiac dysfunction following primary neurological pathology.⁸ Myocardial stunning was revealed with continued interrogation of molecular mechanisms: the density of β_2 -ARs is graded from greatest in the ventricular apex to least in the base, explaining the clinical predominance of the apical ballooning variant.⁹ Single-photon emission computed tomography (SPECT) imaging has demonstrated regional correlation between areas of myocardium experiencing dysfunction and locations with increased sympathetic activity.¹⁰ Microvascular dysfunction has been implicated as a third pathophysiologic contributor to TC given that patients with a history of TC have been found to display heightened vasoreactivity and sympathetic activity in response to acute mental stress when compared to both age-matched controls and those with a history of MI.¹¹

While mechanistically distinct each achieves a sympathogenic state through either an increased direct stimulation of postsynaptic sympathetic neurotransmitters, or following a marked reduction in parasympathetic balance. Guillain-Barré Syndrome causes considerable disruption to autonomic functions. Current evidence suggests up to two-thirds of affected patients will experience some degree of autonomic involvement in the form of blood pressure variations, arrhythmia, vasomotor symptoms, or GI dysmotility.¹² Furthermore, a state of enhanced sympathetic activity has been demonstrated in GBS through measurements of smooth muscle¹³ and dermal sympathetic nerve activity.¹⁴

The association between GBS and TC is rarely observed and past explanations for cardiac involvement often cited emotional stress from rapid respiratory deterioration as the precipitating event. If this were true, one would anticipate a higher incidence of TC within the entire GBS population given that 25% of patients require mechanical ventilation.¹⁵ A higher incidence of TC in the critical care population would also be expected assuming intubation is the emotional trigger. It instead may be diagnostically useful to consider emotional states an emotive indicator of physiological disturbances rather than a precipitating event.

Elevated catecholamines should be regarded as a risk factor for the development of a Takotsubo cardiomyopathy. Recent case reports give examples of Takotsubo cardiomyopathies developing after a variety of catecholamine exposures, and this is especially relevant to the COVID-19 population given the guideline-recommended use of dexamethasone in the treatment of any hospitalized COVID-19 patient requiring more than minimal supplemental oxygen.¹⁶ There have been at least 28 case reports published on Takotsubo Cardiomyopathy in a COVID-19 patient since the start of the outbreak.^{17–24}

Conclusions

There is little doubt Guillain-Barre Syndrome produces the necessary prerequisite conditions for development of a Takotsubo Cardiomyopathy, namely an acute elevation in resting sympathetic tone achieved through multiple potential mechanisms. As evident in the case presented, identification of either syndrome is diagnostically complex; both are multivariable in pathogenesis and diverse in phenotypic presentation. There would likely be practical benefit from future research exploring cardiac dysfunction not only in GBS-like pathologies, but in any condition displaying evidence of severe dysautonomia. As the extant literature would suggest, the highest prospects may lie in the development of a graded classification system via use of clinical, serologic, and radiographic parameters or a combination thereof.

Consent Statement

Institutional approval was not required for publishing the case details.

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Disclosure

The authors report no conflicts of interest in this work.

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