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A Case of Wernicke Encephalopathy Secondary to Anorexia Nervosa Complicated by Refeeding Syndrome and Takotsubo Cardiomyopathy

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 20-year-old
Final Diagnosis: Anorexia nervosa • refeeding syndrome • takotsubo cardiomyopathy • Wernicke encephalopathy
Symptoms: Altered mental status • lethargy • weight loss
Medication: —
Clinical Procedure: —
Specialty: Critical Care Medicine

Objective: Unusual clinical course

Background: Wernicke encephalopathy (WE) is a neurological condition commonly associated with sustained alcohol abuse. However, it should be noted that disorders resulting in severe malnutrition, such as anorexia nervosa (AN), can precipitate nonalcoholic WE. AN is a life threatening psychological and eating disorder defined by inappropriate weight loss from food restriction due to the fear of gaining weight and immoderate desire to be thin. Treatment of those suffering with AN can often be complicated by severe electrolyte derangements after caloric intake termed refeeding syndrome. Although extremely rare, severe cardiomyopathy and ultimately death may occur in patients from AN.

Case Report: Herein describes the case of a 20-year-old female with AN induced WE complicated by refeeding syndrome and hemodynamic compromise in the setting of findings consistent with takotsubo cardiomyopathy. She required ventilatory and hemodynamic support with aggressive intravenous thiamine and phosphorus repletion. Nutritional supplementation was imperative and carefully administered throughout her hospitalization. Her symptoms improved over the course of a few weeks with an ultimate reversal of her cardiomyopathy.

Conclusions: Given the morbidity surrounding AN, practitioners should exhibit caution when caring for those with severe nutritional deficiencies. Clinicians must monitor for severe electrolyte abnormalities and offer aggressive repletion. In addition to electrolyte derangements, severe cardiomyopathy may result as a rare sequela of the aforementioned complications associated with AN. Moreover, it is imperative to understand that patients with AN have the highest mortality of any psychiatric disorder and early intervention is necessary for survival in this vulnerable patient population.

Keywords: Anorexia Nervosa • Refeeding Syndrome • Takotsubo Cardiomyopathy • Wernicke Encephalopathy

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Background

Wernicke encephalopathy (WE) is most often associated with chronic alcohol abuse disorder, however nonalcoholic causes of Wernicke's encephalopathy, such as anorexia nervosa, are also infrequently reported throughout the literature [1-3]. Anorexia nervosa (AN) is a psychiatric disorder characterized by a decreased body mass index (BMI) due to severe food deprivation. Many adverse consequences are seen in AN to include life threatening weight loss, cardiovascular complications, cognitive deficits, and cerebral atrophy. In particular, vitamin B1 (thiamine) deficiency is seen in approximately 38% of individuals with AN leading to a myriad of neuropsychiatric problems including Wernicke's encephalopathy [2]. At least one-third of all deaths in patients with AN are attributed to cardiac causes, mainly sudden cardiac death due to ventricular arrhythmias or cardiogenic shock hypothesized to be secondary to electrolyte abnormalities [4]. Several case reports in the literature have reported the association between Takotsubo cardiomyopathy and AN, but the pathophysiology remains unclear [5].

Refeeding syndrome is also a known complication involved in the treatment of AN which is characterized by abrupt fluid shifts and electrolytes derangements, particularly hypophosphatemia. These biochemical shifts can lead to life threatening consequences and ultimately death [4]. We report an infrequent case of a young female suffering from anorexia nervosa who was diagnosed with nonalcoholic Wernicke's encephalopathy whose hospitalization was complicated by refeeding syndrome and takotsubo cardiomyopathy. It is our hope that this case will bring increased attention to nonalcoholic causes of Wernicke's encephalopathy and the cardiovascular and metabolic complications of AN.

Case Report

The patient is a 20-year-old female who presented to the hospital by family with a chief complaint of decreased oral intake for approximately 2 months. Family noted that over the preceding 2 months the patient had become bed bound and severely deconditioned. The patient felt that eating and ambulation would exacerbate her previous diagnosis of postural orthostatic tachycardia syndrome (POTS). Her past medical history includes POTS, gastroesophageal reflux disease, prior Lyme disease, and worsening anorexia nervosa, purging subtype which she had been diagnosed with since early adolescence. Her outpatient medication regimen included metoprolol tartrate, midodrine, and famotidine, which she was reportedly noncompliant with. Over the preceding weeks prior to her arrival to the hospital it was noticed by the family that the patients purging behavior had increased and she refused to be evaluated by Psychiatry when offered by the family. The

patient had poor follow-up with Psychiatry and her nutritionist for her diagnosis of anorexia nervosa due her denial of her psychiatric condition. However, consistent follow-up was provided by her Cardiologist for POTS who had seen the patient in routine follow-up several months prior to her evaluation in the emergency department.

On arrival to the emergency department the patient's vital signs were unremarkable except for tachycardia. Her weight was 42.1 kg, with a height of 1.626 m for a calculated body mass index of 16.3 kg/m². According to her mother, the patient had lost significant weight over the preceding 2 months. Previously, her weight was 47.4 kg, with a calculated weight decrease of 11.2%. Her physical examination revealed a somnolent, disheveled, and cachectic White woman with dry mucous membranes. She answered questions in short responses with her eyes closed and often refused to answer questions by the examiner. In addition, her pupils were equal and reactive but with dysconjugate gaze and ophthalmoplegia; otherwise, her strength and sensation were intact. Her initial lab work included a complete blood count and basic metabolic panel, which were all unremarkable. The patient was evaluated by crisis screening for psychiatric hospitalization.

While awaiting placement for psychiatric hospitalization, the patient's mother made additional attempts to feed her. The patient did eat a meal throughout the day and became unresponsive shortly thereafter. An emergent computed tomography (CT) of the head was performed and was without acute abnormalities. An arterial blood gas (ABG) was obtained, revealing pH 6.9, pCO₂ 120 mmHg, pO₂ 197 mmHg, and an in-calculable bicarbonate. She was preoxygenation with bagged masked ventilation and was emergently intubated and admitted to the Intensive Care Unit given her change in mental status and inability to protect her airway. Repeat labs revealed a glucose of 126 mg/dL, potassium 3.2 mmol/L, calcium 7.5 mg/dL, magnesium 1.0 mEq/L, phosphate 1.2 mg/dL, albumin 3.0 g/dL, lactate 3 mmol/L, BNP 1085 pg/mL, and troponin 0.46 ng/mL. A plasma thiamine level was not obtained because serum thiamine sensitivity and specificity in symptomatic patients are unclear, and blood levels may not accurately reflect brain thiamine levels; therefore, these results would not have changed clinical management [6]. An electrocardiogram (ECG) revealed sinus tachycardia with ST depressions anteriorly with T wave inversions inferiorly and anterolaterally (**Figure 1**). Magnetic resonance imaging (MRI) was obtained, revealing abnormal T2-weighted signals involving the periaqueductal gray matter extending into the bilateral thalami and medulla without associated enhancement or diffuse restriction; however, mild cortical-based diffusion was noted at the high frontal lobes, consistent with MRI findings of Wernicke encephalopathy (**Figure 2**). An electroencephalogram (EEG) showed diffuse slowing of the dominant rhythm. An echocardiogram was

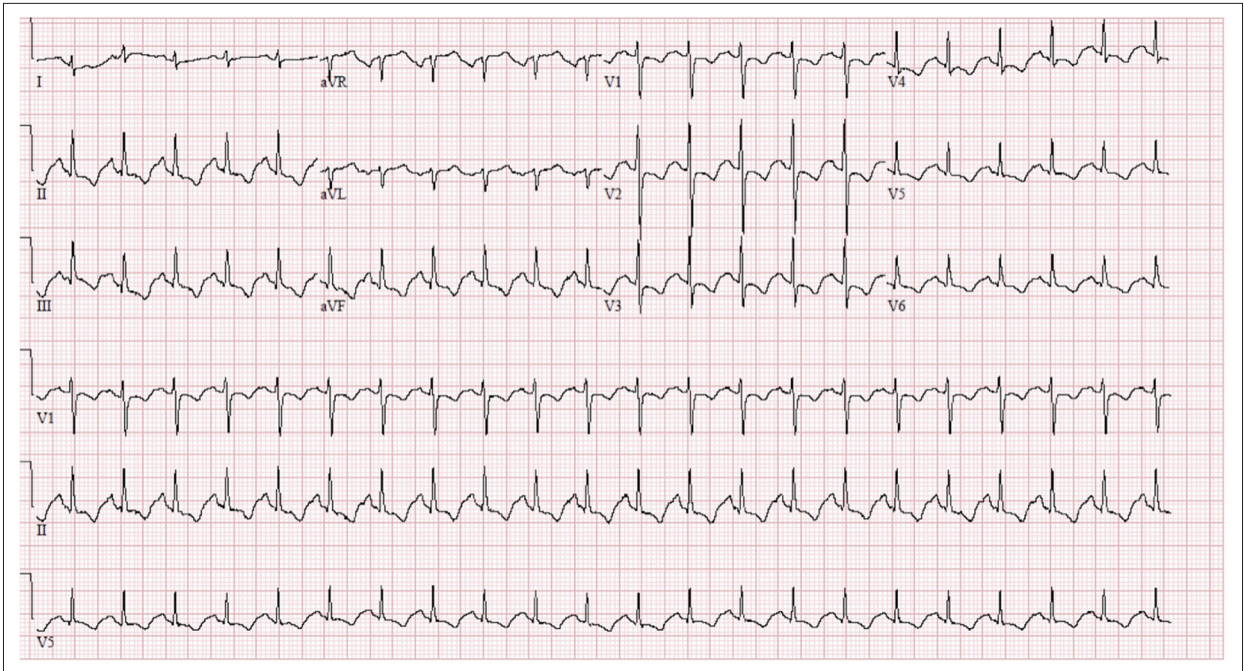


Figure 1. Electrocardiogram revealing sinus tachycardia with ST depressions anteriorly with T wave inversions inferiorly and anterolaterally.

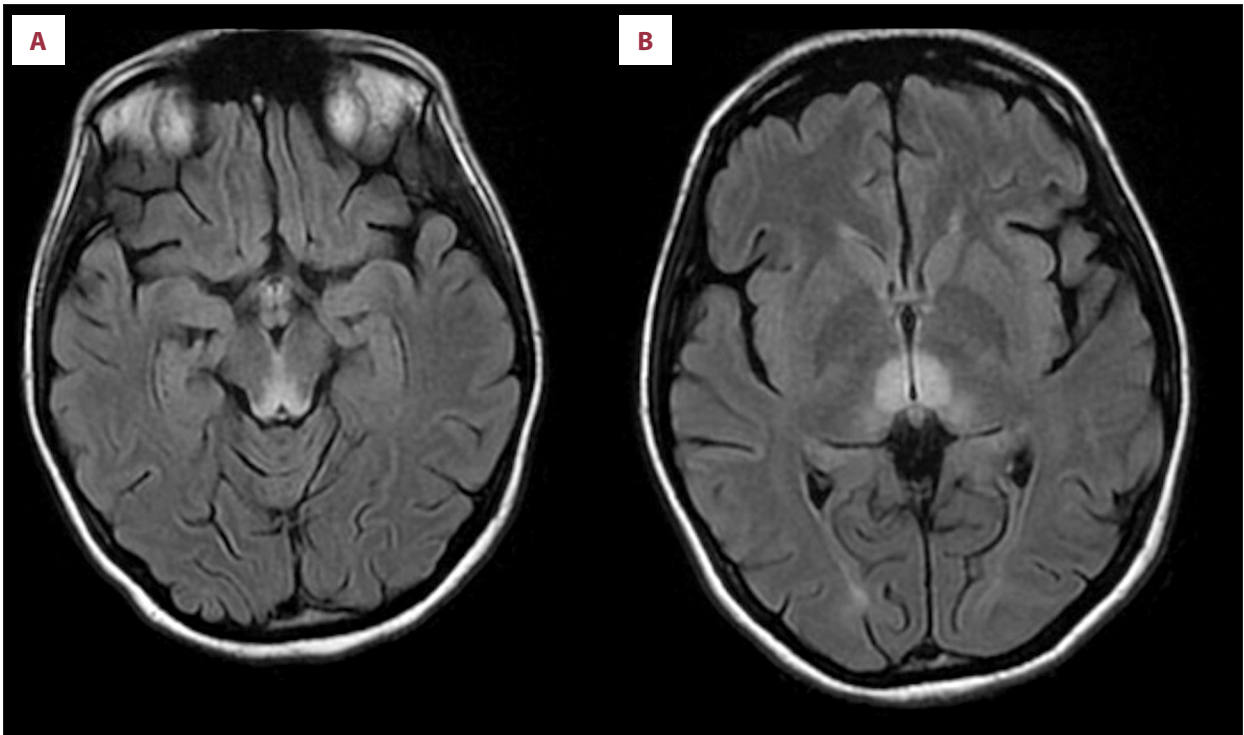


Figure 2. (A) MRI T2 FLAIR image revealing hyper intensity at mammillary bodies. (B) MRI T2 FLAIR image revealing hyperintensity at the thalamus.

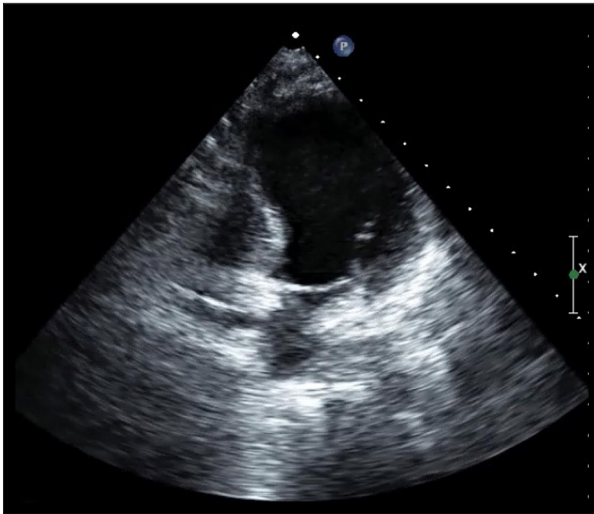


Figure 3. Echocardiogram of apical 4-chamber view with apical ballooning of left ventricle.

done given her ECG changes and elevated cardiac enzymes, revealing severely decreased left ventricular ejection fraction of 20% with global hypokinesia and apical akinesia with ballooning consistent with takotsubo cardiomyopathy (Figure 3). A lumbar puncture (LP) was done due to concern of CNS infection; however, these results were negative.

The patient was supported on the ventilator for several days and supplemented with thiamine, folic acid, multivitamins, phosphate, and magnesium, and was fed slowly with a high-protein and low-carbohydrate tube feeding regimen and was

able to be extubated from the ventilator to room air. Her level of consciousness improved sufficiently to answer questions with her eyes closed; however, her oral intake remained extremely poor and she ultimately required a PEG tube placement for nutrition. A repeat ECG and echocardiogram were obtained after the patient was stabilized, revealing a recovered left ventricular ejection fraction of 60% with resolved apical ballooning (Figure 4). The patient remained in crisis given her severe AN and was discharged to an inpatient psychiatric facility for additional psychiatric rehabilitation. A repeat MRI was performed at 4 weeks after hospital discharge, revealing complete resolution of hyperintensities at the level of mammillary bodies and thalamus (Figure 5).

Discussion

Wernicke encephalopathy (WE) is most commonly caused by thiamine deficiency from chronic alcohol abuse, but nonalcoholic causes of WE, such as malnutrition, are proposed but infrequently reported. Thiamine (also known as vitamin B1) is absorbed in the duodenum and proximal jejunum and is converted to its active metabolite of thiamine pyrophosphate after crossing the blood-brain barrier [7]. Nonalcoholic WE presents a diagnostic challenge for physicians given the low index of suspicion and atypical presentations, leading to a missed diagnosis in 75-80% of cases [3]. Malnutrition should be closely monitored, particularly in anorexic patients with purging behavior, as well as in patients who have recently had bariatric surgery [7]. WE classically presents with ataxia, ophthalmoplegia,

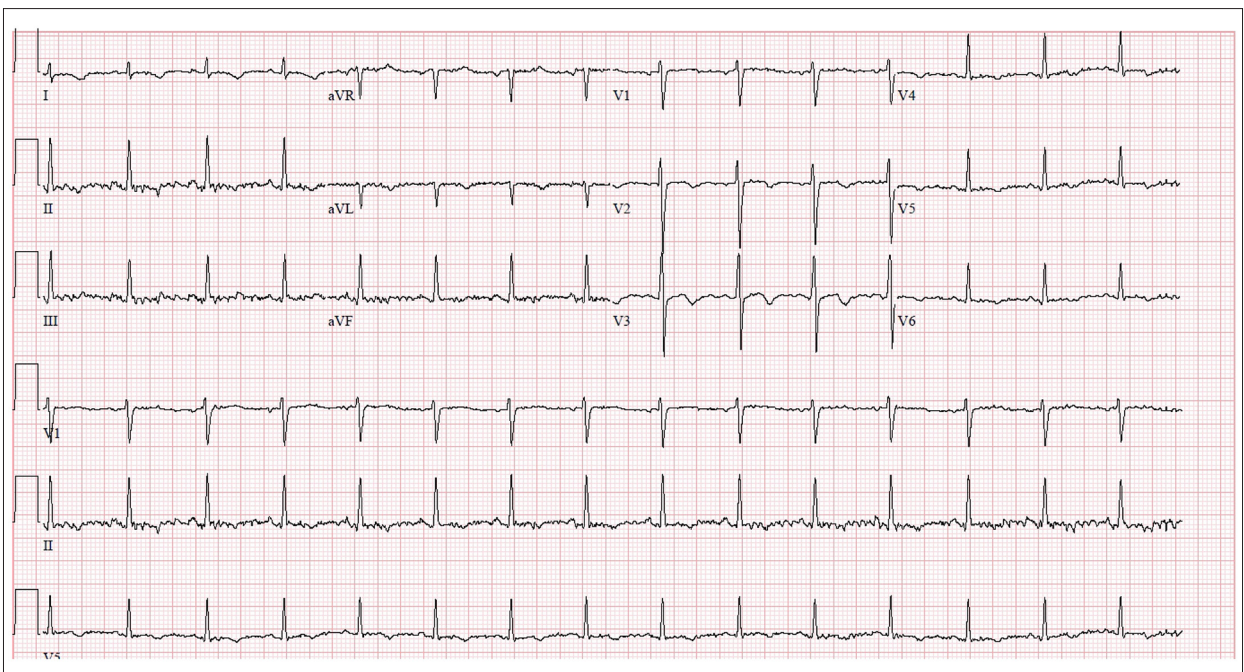


Figure 4. Electrocardiogram revealing near-complete resolution of T wave abnormalities.

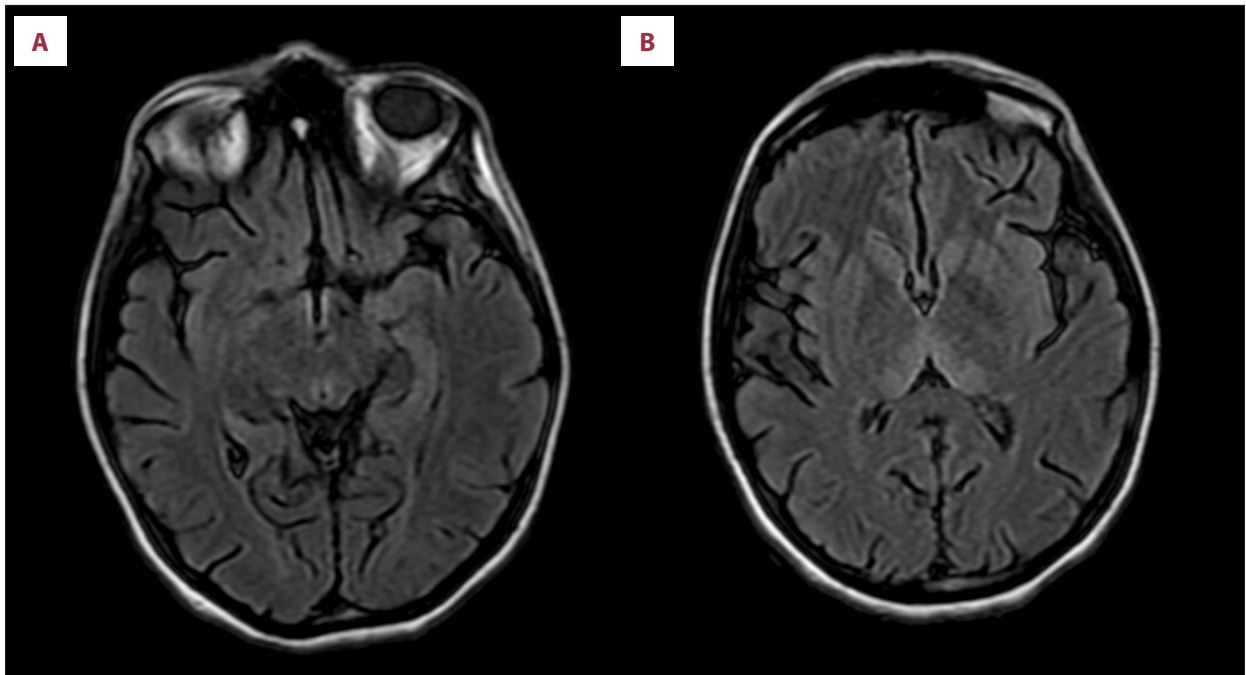


Figure 5. (A) MRI T2 FLAIR image at week 4 follow-up revealing resolution of hyperintensity at mammillary bodies. (B) MRI T2 FLAIR image at week 4 follow-up revealing resolution of hyperintensity at the thalamus.

and global confusion, but this is only present in 16-20% of cases, and atypical presentations are more common in nonalcoholic WE, as in our patient, with lethargy and ophthalmoplegia [1]. Once the diagnosis is suspected, the preferred imaging modality in patients with suspected nonalcoholic WE is MRI, although a normal MRI does not definitely rule out WE [8]. Pathological lesions seen in WE include hyperintensities on the floor of the fourth ventricle, quadrigeminal bodies, periaqueductal gray matter, and mammillary bodies, and medial thalami are commonly reported in the literature. Involvement of the cortex, as in this case, is relatively uncommon and infrequently seen in previous case reports and case studies [9]. Previous studies suggest that WE occurring in patients with AN have a more severe phenotype than in patients with WE induced by chronic alcohol abuse [2].

As noted, WE and AN are due to the severe malnourished state associated with these diseases. The patient's initial ABG derangements can be explained by the absorption of glucose, which is converted to fat through lipogenesis, which can result in a higher respiratory quotient, resulting in increased carbon dioxide production [10]. In such cases, nutritional supplementation must be slowly introduced to avoid rapid fluid and electrolyte shifts, which are the basis of refeeding syndrome [11]. Refeeding syndrome can occur from unbalanced and rapid oral, enteral, or parenteral feeding in chronically malnourished patients such as those with AN [4]. Most of the complications of refeeding syndrome occur due to electrolyte derangements such as hypophosphatemia, hypokalemia, and

hypomagnesemia, resulting in QT interval abnormalities. The QT interval is a measure of myocardial repolarization and a prolonged QT interval is the precursor for an arrhythmogenic substrate, including ventricular arrhythmia and even death [4]. The initial ECG for our patient revealed a correct QT (QTc) interval of 554 ms associated with hypokalemia, hypomagnesemia, and hypophosphatemia, which predisposed this patient to high risk of a sudden cardiac event.

Our patient had neurologic and metabolic sequelae and had a presentation consistent with takotsubo cardiomyopathy (TC). TC is a rare cardiac disorder seen in 1-2% of patients that undergo workup for myocardial injury, and very rarely is associated with AN in the literature. TC mimics the presentation of myocardial infarction without angiographic evidence of vessel occlusion. Typically, echocardiography reveals apical dyskinesia or akinesia with basal hyperkinesia and elevation of cardiac enzymes. These changes are thought to be secondary to intense emotional or physical stressors from catecholamine release [4,12]. Our patient had findings of apical akinesia with ballooning and severe left ventricular dysfunction. It is likely that severe malnutrition over months with the attempted refeeding by family resulted in an elevation in catecholamine levels and, ultimately, myocardial damage. More importantly, treatment of the patient's neurologic condition and metabolic support with refeeding reversed her acquired cardiomyopathy and she returned to baseline cardiovascular function. However, a recent study showed a good early prognosis for patients with low BMI and TC, but mortality at 5-year follow-up was very high [13].

One limitation to the definitive diagnosis of TC in this patient is the absence of the performance of a coronary angiography to exclude obstructive coronary artery disease. Several attempts were made by the consultant cardiologist and intensive care team to obtain informed consent for coronary angiography, but given the patient's age and low pretest probability of ACS, the patient's family decided against this procedure. It is noted in the literature, however, that a small percentage of patients are diagnosed with TC solely on clinical presentation, ECG, cardiac biomarkers, and echocardiographic features. These patients with presumed takotsubo cardiomyopathy have higher in-hospital mortality, likely secondary to misdiagnosis or undertreatment of ACS as TC [14]. The risk of potential ACS and its complications were fully explained to the family as well as the expected resolution of her cardiomyopathy if the correct diagnosis was in fact TC.

We considered an alternative diagnosis of wet beriberi for this patient's decline in cardiovascular function. Wet beriberi, or Shoshin beriberi, is also a complication of thiamine deficiency, which is rarely seen in modern society and may be underdiagnosed in Western countries given the low prevalence of disease. Wet beriberi is characterized by high cardiac output with predominantly right-sided heart failure, hemodynamic instability, and lactic acidosis secondary to thiamine deficiency. The clinical presentation is consistent with signs of heart failure, which includes peripheral edema, elevated JVD, and, rarely, cyanosis of distal extremities [15]. A diagnosis of TC was made in our patient given the absence of hemodynamic instability after initial resuscitation, as well as echocardiographic evidence of apical ballooning, with prompt and complete recovery of ejection fraction, which is more consistent with TC.

Treatment of this patient was multifactorial as she required mechanical ventilation due to her initial inability to protect her airway. Once ventilatory support was provided, she was supplemented with thiamine and slowly fed to avoid worsening of her refeeding syndrome. Thiamine is known to play an important role in glucose metabolism, which is aggravated by hypomagnesemia, as magnesium is a cofactor for thiamine-dependent enzymes [16]. Thiamine is recommended for

patients with a diagnosis consistent with WE; however, the optimum dose, frequency, and duration have not been supported by substantial evidence. Despite this recommendation, early thiamine administration is recommended and clinicians should have a low threshold for initiation [8]. It is recognized that lower doses of daily thiamine may not help to restore the deficiency, improve clinical signs, or prevent mortality [5]. Our patient was treated with 250 mg IV thiamine daily as well as multivitamins and folic acid for her diagnosis of nonalcoholic WE until resolution of her decreased mental status, and she was transitioned to oral thiamine, multivitamin, and folic acid supplementation upon discharge to a psychiatric facility. Her decreased left ventricular function of 20% and ECG changes resolve during her hospital stay and returned to her baseline left ventricular ejection fraction of 60%.

Our case is unique because she simultaneously had many of the rare complications of anorexia nervosa, such as refeeding syndrome, takotsubo cardiomyopathy, and nonalcoholic Wernicke encephalopathy. This case demonstrates the complexity and morbidity that physicians must be aware of when treating severely malnourished patients. These patients are at increased risk for sudden death, most often related to cardiovascular sequelae secondary to fluid and electrolyte shifts from refeeding [4].

Conclusions

AN has the highest mortality of any psychiatric disorder and can cause a variety of complications that physicians must be cognizant of while treating these patients [2]. As demonstrated with our patient, cardiovascular dysfunction is the most life threatening. Our case also demonstrates many of the complications that can arise when treating a patient with AN, which is rarely reported in the literature. Early detection of WE and treatment with thiamine is very important, as these patients can progress to Korsakoff syndrome, which has an even higher mortality rate [1]. Early intervention and prompt treatment can change the course of this disease, prevent patient suffering, and provide a chance for functional recovery.

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