

Defining Features of Patients who Develop Takotsubo Cardiomyopathy during Myasthenic Crisis: A Systematic Review of Case Studies

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Received April 29, 2019; Revised June 09, 2019; Accepted July 19, 2019

Abstract Background. Myasthenic crisis can induce Takotsubo cardiomyopathy leading to transient systolic and diastolic left ventricular dysfunction and wall-motion abnormalities, including the characteristic apical ballooning. We aimed to define the clinical features of this disease entity. **Methods.** A systematic review was conducted to examine the characteristics of Takotsubo cardiomyopathy presenting in myasthenia gravis patients. Case reports were accessed by searching MEDLINE/PubMed, Google Scholar, CINAHL, and Web of Science databases. 523 articles were identified and 14 were selected for review. **Results.** Takotsubo cardiomyopathy presenting in myasthenia gravis' patients tends to affect women between the ages of 40 to 77. History of atrial fibrillation or hypertension was found in a minority of cases. Generalized weakness, fatigue, dysphagia and respiratory distress were common at presentation. Vital signs demonstrated normal blood pressure without tachycardia or bradycardia. Elevated values of troponins, creatine kinase (CK), and CK-MB isoenzymes were recorded. ST-segment elevation followed by T-wave inversion were predominantly found on electrocardiograms. Apical abnormalities in the form of ballooning, hypokinesia, or sparing and reduced left ventricular ejection fraction ($\leq 45\%$) were observed using transthoracic echocardiogram or left ventriculography. Coronary angiography demonstrated no obstructive lesions. Ventilatory support, cholinesterase inhibitors and glucocorticoids resulted in the recovery or improvement of the left ventricular ejection fraction and hemodynamic stability. Only a minority of patients died of refractory heart failure. Treatment with inotropes and/or vasopressors led to poorer outcomes, including death or intractable heart failure. **Conclusion.** The management of Takotsubo cardiomyopathy developing in myasthenia gravis patients should focus on addressing the myasthenic crisis, while providing supportive care in an intensive care setting.

Keywords: *takotsubo cardiomyopathy, myasthenic crisis*

Cite This Article: Pramod Theetha Kariyanna, Bayu Sutarjono, Apoorva Jayarangaiah, Remi Okwechime, Amog Jayarangaiah, Perry Wengrofsky, and Isabel M. McFarlane, "Defining Features of Patients who Develop Takotsubo Cardiomyopathy during Myasthenic Crisis: A Systematic Review of Case Studies." *American Journal of Medical Case Reports*, vol. 7, no. 9 (2019): 203-209. doi: 10.12691/ajmcr-7-9-6.

1. Introduction

Takotsubo cardiomyopathy is characterized by transient systolic and diastolic left ventricular dysfunction with a variety of wall-motion abnormalities, most commonly the ballooning of the left ventricular apex [1]. This syndrome has been given the name of "Takotsubo," or Japanese octopus trap [2]. Patients with Takotsubo cardiomyopathy present with substernal chest pain and dyspnea that

resembles acute coronary syndrome. There can be associated electrocardiographic abnormalities such as ST-segment elevation, T-wave inversion, QT-prolongation, or abnormal Q-waves. There can also be elevated cardiac troponin. It is a diagnosis of exclusion, after pheochromocytoma or myocarditis have been ruled out.

Although previous studies have suggested that Takotsubo cardiomyopathy is predominantly preceded by emotional triggers, subsequent reports indicate that this syndrome may also occur with physical triggers. A recent

study concluded that the prevalence of physical triggers exceeds that of emotional triggers [1]. For patients with myasthenia gravis, this physical trigger is a cholinergic crisis.

Myasthenia gravis is an autoimmune neuromuscular disorder in which antibodies bind to acetylcholine receptors or to functionally related molecules in the post-synaptic membrane at the neuromuscular junction causing muscle weakness and fatigue [3]. Typically, there is fluctuating and fatigable extraocular (e.g. diplopia, ptosis) and bulbar (dysarthria, dysphagia) muscle weakness. Symmetrical proximal weakness involving the neck (e.g. difficulty holding up the head) and upper extremities (e.g. difficulty combing hair) is also seen. Sensation, reflexes, muscle bulk/tone, and autonomic function are usually intact.

Precipitating stress caused by infection (e.g. pneumonia), surgery, or various medication (e.g. azithromycin) may lead to high levels of circulating catecholamines leading to myasthenic crisis, characterized by acute deterioration in bulbar and respiratory muscles, which can lead to respiratory failure requiring mechanical ventilation [3] and possibly stress-induced cardiomyopathy.

Myasthenia gravis occurs in 1: 7500 individuals, affecting women during the second to third decade and men in their fifth and sixth decade of life [4]. One study reported that 16% of patients with myasthenia gravis exhibit several types of cardiac involvement, ranging from asymptomatic electrocardiogram changes to myocarditis, heart failure, and sudden death [5]. Currently, there is scanty research on the topic of patients with Takotsubo cardiomyopathy induced by myasthenic crisis [6]. This systematic review aimed to determine the characteristics of patients with takotsubo cardiomyopathy and myasthenia gravis based on existing case reports, as well as recovery and outcomes following treatment.

2. Methods

2.1. Protocol and Registration

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, found in Supplementary Table 1, was utilized to for this systematic review. The protocol was not registered.

Table 1. Summary of descriptive characteristics of included articles (n=14)

Reference, publication year	Country, Study Design	Patient profile (age in years, sex)	Review of symptoms	Diagnosis	Hemodynamically stable and normalization or improvement of ejection fraction upon discharge
Anand US et al, 2013 [7]	India, case report	50, female	Dysarthria, Dysphagia, Generalized weakness and fatigue, Myalgia, Pulmonary edema, Respiratory distress, Paralysis, Ptosis or diplopia, Other (ANA and dsDNA positive)	Initial presentation of myasthenic crisis, developed takotsubo cardiomyopathy and pulmonary edema	Yes
Bansal V et al, 2011 [8]	USA, case report	77, male	Dysarthria, Dysphagia, Generalized weakness and fatigue, Respiratory distress, Ptosis or diplopia, Other (Anxiety, Seizures)	Initial presentation of myasthenic crisis, developed takotsubo cardiomyopathy	Yes
Battineni A et al, 2017 [9]	USA, case report	69, female	Chest pain, Dysarthria, Generalized weakness and fatigue, Hypertension, Respiratory distress, Ptosis or diplopia, Other (Grave's disease)	Initial presentation of myasthenic crisis, developed takotsubo cardiomyopathy	Yes
Beydoun SR et al, 2010 [10]	USA, case report	60, female	Dysphagia, Generalized weakness and fatigue, Respiratory distress, Ptosis or diplopia	Initial presentation of myasthenic crisis, developed takotsubo cardiomyopathy	Yes
Bijulal S et al, 2009 [11]	India, case report	40, female	Generalized weakness and fatigue, Pulmonary edema, Respiratory distress	Initial presentation of myasthenic crisis after removal of invasive thymoma, developed takotsubo cardiomyopathy and pulmonary edema	No (No improvement of ejection fraction, died on day 6 due to refractory heart failure and multi-organ damage)
Douglas TM et al, 2018 [12]	USA, case report	49, male	Respiratory distress	Initial presentation of myasthenic crisis after thymectomy, developed takotsubo cardiomyopathy	Yes (Developed decompensated heart failure after discharge)
Finsterer J et al, 2018 [13]	Austria, case report	76, female	Dysarthria, Myalgia, Hypertension, Pulmonary edema, Respiratory distress, Other (Atrial fibrillation, Polymyositis)	Initial presentation of myasthenic crisis after resection of thymoma, developed takotsubo cardiomyopathy and pulmonary edema, incidental finding of thymoma	No (No improvement of ejection fraction, died on day 108 due to malignancy)

Reference, publication year	Country, Study Design	Patient profile (age in years, sex)	Review of symptoms	Diagnosis	Hemodynamically stable and normalization or improvement of ejection fraction upon discharge
Harries IB et al, 2015 [14]	UK, case report	70, male	Dysarthria, Dysphagia, Generalized weakness and fatigue, Hypertension, Pulmonary edema, Respiratory distress, Other (Polymyalgia rheumatics)	Initial presentation of myasthenic crisis, developed takotsubo cardiomyopathy and pulmonary edema	Yes
Hirose K et al, 2008 [15]	Japan, case report	63, female	Dysphagia, Respiratory distress, Other (Atrial fibrillation)	Initial presentation of myasthenic crisis, developed takotsubo cardiomyopathy, QT prolongation and Torsades de Pointes	No (Improvement of ejection fraction, but died on day 70 due to sepsis and disseminated intravascular coagulation)
Nishinarita R et al, 2012 [16]	Japan, case report	52, female	Generalized weakness and fatigue, Respiratory distress, Ptosis or diplopia	Initial presentation of myasthenic crisis, developed takotsubo cardiomyopathy, incidental finding of thymoma	Yes
Sousa JM et al, 2005 [17]	Brazil, case report	64, male	Chest pain, Generalized weakness and fatigue, Respiratory distress	Initial presentation of myasthenic crisis, developed takotsubo cardiomyopathy	No (Improvement of ejection fraction, but died after 1 month due to multisystem organ failure secondary to sepsis)
Thanaviratnanich S et al, 2014 [18]	USA, case report	42, female	Dysphagia, Respiratory distress	Initial presentation of myasthenic crisis after resection of malignant thymoma that invaded pericardium, developed takotsubo cardiomyopathy	Yes
Valbusa A et al, 2013 [19]	Italy, case report	75, female	Dysarthria, Dysphagia, Generalized weakness and fatigue, Respiratory distress, ptosis or diplopia, Other (Atrial fibrillation)	Initial presentation of myasthenic crisis, developed takotsubo cardiomyopathy, QT prolongation and Torsades de Pointes	Yes
Wong CP et al, 2012 [20]	Singapore, case report	64, female	Chest pain, Generalized weakness and fatigue, Respiratory distress	Initial presentation of myasthenic crisis, developed takotsubo cardiomyopathy	Yes

2.2. Eligibility Criteria

Inclusion Criteria. Only articles that reported the association of myasthenia gravis and Takotsubo cardiomyopathy were included.

Exclusion Criteria. Studies were excluded if: (1) they were not case reports or case series, (2) they were not peer-reviewed, or (3) they were not in English.

2.3. Information Sources and Search Strategies

A comprehensive literature search using MEDLINE/PubMed, Google Scholar, CINAHL, and Web of Science databases up to and including 30 October 2018. The terms “Takotsubo,” “Tako-Tsubo,” “stress cardiomyopathy(ies),” “stress induced cardiomyopathy(ies),” or “apical ballooning” were selected in combination with the words “myasthenia,” “myasthenic,” “gravis,” or “crisis” for the complete search strategy, which is found in Supplementary Material.

2.4. Study Selection

Initial triage of articles was based on whether titles or abstracts met the inclusion criteria. Full-text articles were then read, and those that did not satisfy the inclusion/exclusion criteria were excluded.

2.5. Data Collection Process and Data Items

Data extracted from articles included the name of first author, year of publication, country, and study design. Variables for which data were sought included the age and sex of the patient, past medical history, past surgical history, chief complaints, intubation, medications, electrocardiography results, transthoracic electrocardiogram results including ejection fraction, pertinent radiology results, peak troponin values, peak creatine kinase values, peak creatine kinase-muscle/brain values, peak acetylcholine receptor antibodies, outcome, and follow-up.

2.6. Synthesis of Results and Summary of Measures

Data were tabulated, evaluated, and summarized.

2.7. Risk of Bias across Studies

Potential bias across studies were analyzed within study characteristics.

3. Results

3.1. Study selection

From 4 databases, 523 articles were selected. Based on relevance to myasthenia gravis and Takotsubo cardiomyopathy, 25 were selected. Only 14 articles complied with the study selection criteria [7-20]. A PRISMA flow diagram detailing the process of identification, inclusion, and exclusion of studies is shown in Figure 1.

3.2. Study Characteristics

A summary of study characteristics is given in Table 1. All studies were case reports published between 2005 and 2018. USA [8,9,10,12,18] and Asia [7,11,15,16,20] each conducted 5 studies, while 3 took place in Europe [13,14,19]. South America contributed to 1 study only [17].

3.3. Results of Individual Studies

A summary of findings is given in Table 2.

All studies described patients who were admitted for myasthenic crisis who then developed Takotsubo cardiomyopathy. 5 articles did not mention any other complications [8,9,10,17,20]. Five articles emphasized a previous history of thymectomy [12] or thymoma [11,13,16,18]. The gradings for thymomas were B1 [16] or B2 [13,18]. 4 articles observed pulmonary edema as a complication during the myasthenic crisis [7,11,13,14], while 2 articles reported QT prolongation and Torsades de Pointes [15,19]. Only 1 article reported polymyositis [13] as a possible diagnosis.

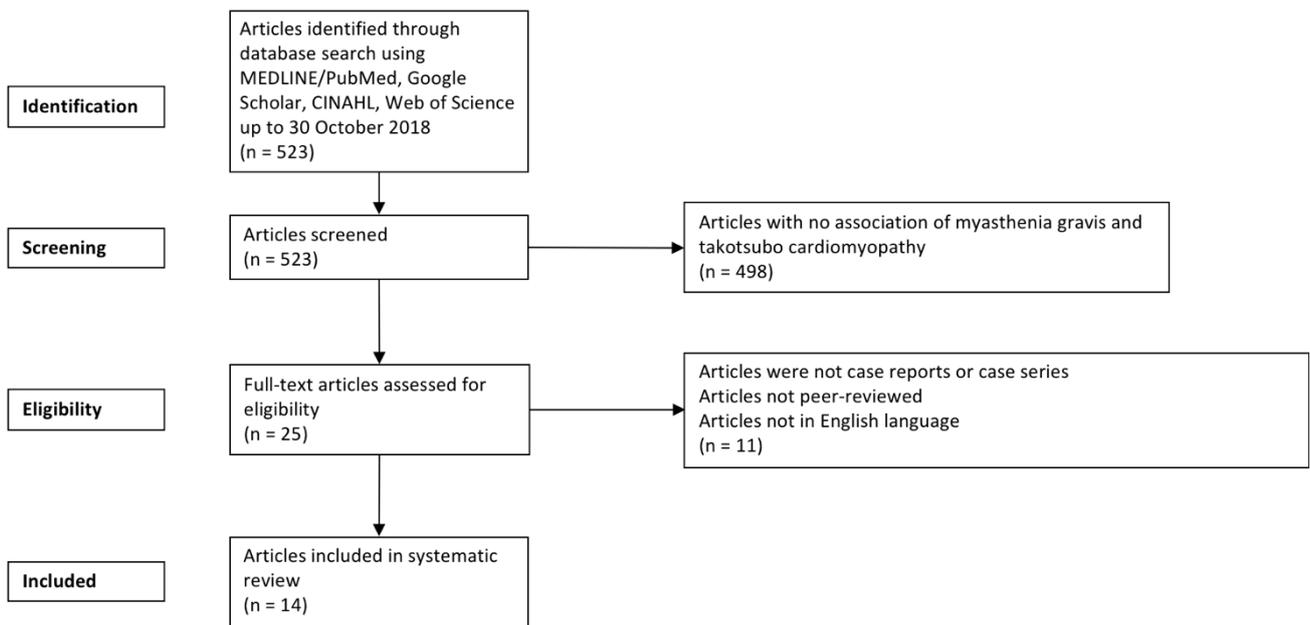


Figure 1.

Table 2. Results of tests and diagnostics

Reference	Heart rate	Blood pressure	ST changes	T changes	QT prolongation and Torsades de Pointes	Peak troponin (ng/mL)	Peak CK (IU/L)	Peak CK-MB (IU/L)	ACh-R Ab (nmol/L)	Apical ballooning or dyskinesia, akinesia, hypokinesia, or sparing	Basal function	Ejection fraction (%)	Coronary angiography
Anand US et al [7]	↑	↓	Depression (I, aVL, V5, V6)	Inversion (I, aVL, V5, V6)	-	0	-	21	-	Hypokinesia	-	35	-
Bansal V et al [8]	-	-	Elevation (V3-V4)	-	-	1.83	161	9.4	6.8	Hypokinesia	-	<20	-
Battineni A et al [9]	-	-	Elevation (V1-V4)	-	-	0.32	-	-	-	Ballooning and akinesia	-	20-30	No new coronary lesions

Beydoun SR et al [10]	-	-	Elevation (V2)	-	-	2.5	-	-	252.45	Ballooning and sparing	Hyperdynamic proximal section	32-40	No significant CAD
Bijulal S et al [11]	-	↓	-	Inversion (I, aVL, V3, V4)	-	>0.39	-	<25	-	Ballooning and akinesia	Hyperkinetic basal segments	32	Normal
Douglas TM et al [12]	↑	-	-	Inversion (II, III, aVF, V2-V6)	-	2.47	-	-	-	Ballooning and hypokinesia	Normal	30-35	Widely patent coronaries with mild lumen abnormalities
Finsterer J et al [13]	↑	-	-	-	-	1.82	2210	-	6.48	Ballooning	-	Reduced	Normal
Harries IB et al [14]	-	-	Elevation (widespread)	-	-	>100	-	-	>0.1	Hypokinesia	Normal	-	Unobstructed coronary arteries
Hirose K et al [15]	↑	-	-	Inversion (I, aVL, V1-V6)	Yes	4.4	29	-	0.3	Ballooning and akinesia	-	-	-
Nishinarita R et al [16]	-	-	Elevation (I, II, aVL, V2, V5, V6) Depression (III, aVR, V1)	-	-	-	266	40	48	Ballooning and sparing, akinesia	hyperkinesia of proximal segments, hyperdynamic	45	Normal
Sousa JM et al [17]	-	↓	Elevation (V1-V6)	-	-	9.6	-	22	-	Ballooning and dyskinesia	Hypokinesia of basal segments	20	No severe obstructive lesions
Thanaviratana nich S et al [18]	↑	-	-	-	-	0.185	<199	-	>80	Sparing	-	15	-
Valbusa A et al [19]	-	-	-	Inversion (V3-V6)	Yes	2.46	-	-	-	Ballooning	-	15	Normal
Wong CP et al [20]	-	-	x	-	-	6.73	266	-	-	Ballooning and akinesia	hypercontractile basal region	30	Minor CAD

3.4. Synthesis of Results

Patient profile. The patients' age ranged between 40 to 77-years. The average age for all studies was 60.9 years. Adjusting for location, the average age for American studies was 62.4 years, while Asian studies averaged 53.8 years. The average age for European studies was 73.7 years. 4 articles described male patients with an average age of 64.1 years [8,12,14,17], while the remaining 10 studies of female patients had an average age of 60.5 years [7,9,10,11,13,15,16,18,19,20]. Common medical history aside from myasthenia gravis and change in thyroid function included atrial fibrillation [13,15,19] and hypertension [9,13,14]. Grave's disease [9] and polymyalgia rheumatica [14] were reported affecting 1 patient each.

Presenting complaints. All studies reported respiratory distress, which encompassed breathlessness, shortness of breath, wheezing, respiratory failure, or respiratory muscle paralysis [7-20]. The next common presentation was generalized weakness and fatigue (71.4%) [7-11,14,16,17,19,20] followed by dysphagia (57.1%) [7,8,9,10,14,15,18,19] and then equally ocular problems involving either ptosis or diplopia [7,8,9,10,16,19] or dysarthria (42.9%) [7,8,9,13,14,19]. Chest pain was only reported in 21.4% of the cases [9,17,20]. Tachycardia was recorded in 35.7% of patients [7,12,13,15,18], while only three patients presented with hypotension [7,11,17].

Laboratory tests. Seven articles reported positive assays for acetylcholine receptor antibodies with values ranging from 0.3 to 252.4 nmol/L [8,10,13,14,15,16,18]. All of the studies except for one [16] reported troponin

values. Two studies measured values between 0.04 and 0.39 ng/mL [9,18], while the remaining 11 studies observed values greater than 0.39 ng/mL [8,10-17,19,20]. Six studies reported creatine kinase levels, only one reported a value within normal limits [18]. The remaining studies recorded creatine kinase values ranging from 29 to 2210 IU/L [8,13,15,16,18,20]. Five studies reported creatine kinase-muscle/brain values (CK-MB). Only one was within normal limits [11], while the remaining four articles ranged from 9.4 to 40 IU/L [7,8,16,17].

Diagnostic studies. Only two patients had normal sinus rhythm [13,20]. 42.9% of EKG recordings demonstrated ST-segment elevations [8,9,10,14,16,17], while only two patients presented with ST-segment depression [7,16]. One patient presented with both ST-segment elevation and ST-segment depression [16]. T-wave inversions were observed in 35.7% of patients [7,11,12,15,19], while two patients developed QT prolongation and Torsades de Pointes [15,19]. Transthoracic echocardiogram revealed apical abnormalities in all patients in the form of ballooning [9,10,11,13,15,19], dyskinesia [17], hypokinesia [7,8,12,14], akinesia [9,11,15,16,20], or sparing [10,18]. Four patients showed hyperkinetic basal function [10,11,16,20], while only one patient exhibited hypokinetic basal function [17]. Eight patients underwent left ventriculography, revealing apical dysfunction in the form of ballooning [10,11,12,13,16,17,20], hypokinesia [9,12], or sparing [10,16], while half of the patients demonstrated hyperkinetic basal function [10,11,16,20]. Coronary angiography was conducted on 10 patients; all studies reported either normal coronaries [11,13,16,19] or non-severe obstructive lesions [9,10,12,14,17,20].

Evolution of myasthenia crisis and takotsubo cardiomyopathy. Following the development of the myasthenic crisis, 85.7% of patients required intubation and supportive ventilation [7,8,10-18,20]. Only two studies did not report left ventricular ejection fraction values [14,15]. All others described a reduction of the ejection fraction that ranged from 45% to 15% of the systolic function [7-13,16-20]. The LVEF improved in 66.7% of the patients [7,8,9,10,16,17,19,20], while in 16.7% of the cases, a substantial improvement was reported [12,18].

Management of myasthenic crisis and Takotsubo cardiomyopathy. Cholinesterase inhibitors, in the form of Neostigmine or Pyridostigmine, were used in 78.6% of the cases. [7,8,10-16,19,20], and 64.3% received glucocorticoids [7,8,10,12,14,15,16,18,19]. Plasmapheresis [8,9,10,17], intravenous immunoglobulin [7,12,14,18], and immunosuppressants [8,16,18] were administered in a minority of patients. Finally, inotropes and/or vasopressors were used in over a third of patients [7,11,12,13,17].

Outcome. 71.4% of the patients recovered [7,8,9,10,12,14,16,18,19,20] and were hemodynamically stable to be discharged home or transferred to sub-acute care facilities. Survival outcome rates were higher for patients who received cholinesterase inhibitors (72.7%), glucocorticoids (88.9%), plasmapheresis (75%), intravenous immunoglobulin (100%), or immunosuppressants (100%), compared to patients who were managed with inotropes and/or vasopressors (40%). One patient on inotropes and/or vasopressors, later developed decompensated heart failure [12]. Of the patients that did not recover, one patient died six days after admission [11] due to refractory heart failure, while all others died after a prolonged stay beyond 30 days due to sepsis [15,17] or malignancy [13].

3.5. Risk of Bias across Studies

Due to the nature of descriptive studies, the results being presented are liable to investigator, procedure, and selection bias. The small sample size limits the feasibility of statistical calculations.

4. Discussion

Although this is not the first review to attribute Takotsubo cardiomyopathy to myasthenic crisis [6], it is the first systematic review to provide a comprehensive picture of patients concurrently afflicted by the two disorders. This systematic review revealed that those affected were mostly women between the ages of 40 and 77 years. A minority of patients had a history of atrial fibrillation or hypertension. The patients presented with respiratory distress, generalized weakness and fatigue, and dysphagia. Blood pressure was within normal range and neither tachycardia or bradycardia were observed. Laboratory tests revealed elevated troponin, CK, and CK-MB values. EKG changes consisted of ST-segment elevation followed by T-wave inversion. Apical abnormalities in the form of ballooning, hypokinesia, or sparing and reduced left ventricular ejection fraction were observed during the transthoracic echocardiogram or left ventriculography. Coronary angiography demonstrated no

obstructive lesions. Patients were intubated and treated with cholinesterase inhibitors and glucocorticoids, which resulted in the recovery or improvement of ejection fraction and hemodynamic stability. Only a very small minority died of refractory heart failure. Over a third of the patients were treated with inotropes and/or vasopressors, leading to high mortality or intractable heart failure.

Myasthenia gravis-related clinical heart disease and heart dysfunction are very rare even though functional imaging studies have shown minor and sub-clinical dysfunction [21]. In population-based studies, myasthenia gravis has not been associated with an increase in mortality related to heart disease [22]. For example, although myocarditis is found in increased frequency in patients with myasthenia gravis, it is still a rare finding [4]. Acute myocarditis can mimic Takotsubo due to their similar clinical presentation. In some cases, acute myocarditis presents with similar regional left ventricular wall motion abnormalities [21]. It is unknown whether there are similar mechanisms attributed to both myocarditis and Takotsubo cardiomyopathy.

Comparison of the common features of a patient with myasthenic crisis and Takotsubo cardiomyopathy, to patients with takotsubo cardiomyopathy only at baseline, reveal only few striking differences. Chest pain was not a prominent feature in the systematic review, but respiratory distress was. Neurologic or psychiatric disorders afflicted nearly half of patients in the Templin et al. study [1], whereas a single patient had a past medical history of depression [19]. Ventilation was required by 17.3% of patients in the Templin et al. study [1], whereas all patients in the systematic review required intubation and mechanical ventilation due to respiratory collapse from myasthenic crisis.

It is questionable whether medical treatment influences the outcome after the acute phase of takotsubo cardiomyopathy. Our data suggest that the management of myasthenic crisis contributed to the recovery of the clear majority of patients, whereas the use of inotropes and/or vasopressors resulted in poorer outcome. The mortality rate of patients in myasthenic crisis (4.47%) [23] or major adverse cardiac and cerebrovascular events within 30 days after hospital admission of patients with takotsubo cardiomyopathy (7.1%) [1] are similar to the mortality rate of heart-related causes as determined by this systematic review (7.1%).

A characteristic feature of Takotsubo cardiomyopathy is the spontaneous resolution of left ventricular wall motion within hours to weeks [24]. The management in the acute stage during myasthenic crisis should be no different. Therefore, treatment should be supportive and focus on resolving complications of the myasthenic crisis. Patients with worsening weakness who require intubation should receive fast-acting immunosuppressive agents and admission to an intensive care unit. Intravenous immunoglobulin and plasmapheresis are regarded equally effective in treating severe myasthenia gravis [25].

There are multiple limitations to this systematic review including small sample size of available cases and the lack of long term follow-up and outcomes.

In conclusion, this systematic review unveiled the pertinent clinical characteristics of Takotsubo cardiopathy

occurring during myasthenic crisis. The therapies employed in the cases reinforces the need to focus on addressing the myasthenic crisis, in order to allow for a full recovery for this complex patients.

Acknowledgements

This work is supported, in part, by the efforts of Dr. Moro O. Salifu M.D., M.P.H., M.B.A., M.A.C.P., Professor and Chairman of Medicine, State University of New York- Downstate Medical Center through NIH Grant number S21MD012474.

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Supplementary 1

Complete search strategy

The search strategy was adapted for each database. The complete search strategy was as follows:

(Takotsubo OR tako-tsubo OR stress cardiomyopathy OR stress cardiomyopathies OR stress induced cardiomyopathy OR stress induced cardiomyopathies OR apical ballooning) AND (myasthenia OR gravis OR myasthenic OR crisis)



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