International Journal of Cardiology 153 (2011) 241–248

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Takotsubo-like cardiomyopathy in pheochromocytoma ☆

Vikram Agarwal [a], Gunjan Kant [a], Nidhi Hans [b], Franz H. Messerli [a,*]

[a] Division of Cardiology, St. Luke's-Roosevelt Hospital Center, Columbia University College of Physicians and Surgeons, New York, New York, United States
[b] Harvard School of Public Health, Boston, Massachusetts, United States

ARTICLE INFO

Article history:
Received 29 November 2010
Received in revised form 3 March 2011
Accepted 11 March 2011
Available online 7 April 2011

Keywords:
Takotsubo cardiomyopathy
Stress cardiomyopathy
Pheochromocytoma
Cardiomyopathy
Review

ABSTRACT

Background: Takotsubo Cardiomyopathy (TTC) is commonly triggered by acute illness, physical or emotional stress and has been associated with elevated catecholamine levels. TTC has also been associated with pheochromocytoma (TTC-pheo).
Methods: We performed a computer assisted search of the electronic databases Medline, Scopus and Google Scholar from 1965 to January 2011. All case reports with reported TTC-pheo were selected and compared to a recent review by Gianni et al. which examined primary TTC (TTC-primary).
Statistics: Data analysis was performed using SPSS version 18. Chi-square test of Fisher's exact test was used as appropriate to compare categorical data.
Results: 38 cases of TTC-pheo were retrieved from literature and compared to 254 cases of TTC-p. Chest pain was the most common presentation in both groups. The TTC-pheo patients were on average 18 years younger than patients with TTC-p ($p<0.01$). Only a minority of TTC-pheo patients presented with classical features of pheochromocytoma including hypertension (52.6%), headache (28.9%), palpitations (31.6 %), and diaphoresis (26.3%). In TTC-pheo complications rates were higher compared to TTC-p, including cardiogenic shock (34.2% vs. 4.2%, $p<0.01$) and heart failure (46.7% vs. 17.7%, $p<0.01$). Antecedent stressors were less common in TTC-pheo. About one-third of TTC-pheo patients presented with the inverted pattern, which compared to the apical pattern, was associated with higher complication rates, including, cardiogenic shock, heart failure, acute renal failure and arrhythmias.
Conclusions: Although rare, pheochromocytoma should be considered in the differential diagnosis of TTC especially in younger patients presenting without antecedent stressors and a high complication rate. The similarities in the clinical features and outcomes in patients with TTC-p and TTC-pheo point to a similar underlying cardiac pathophysiologic process at the time of the acute presentation.

1. Introduction

Most cases of Takotsubo cardiomyopathy (TTC) are triggered by acute medical illness or intense physical or emotional stress. Although its underlying pathophysiology remains uncertain, it has been hypothesized that stress related neurohumoral factors, especially catecholamines, play an important role in its pathogenesis. Two sets of diagnostic criteria have been proposed to aid in the diagnosis of TTC; one is by the Mayo Clinic [1] and the other by the Takotsubo Cardiomyopathy Study Group [2]. While both guidelines agree about the unknown underlying pathophysiology, the Takotsubo Cardiomyopathy group guidelines recognize the occurrence of Takotsubo-like myocardial dysfunction, a cardiac presentation similar to TTC in known catecholamine excess states, including pheochromocytoma and cerebrovascular accidents, while the Mayo Clinic excludes these patients. Even in the revised Mayo Clinic guidelines, pheochromocytoma continues to be an exclusion criterion for the diagnosis of stress cardiomyopathy [3]. Recently published review articles on TTC have focused on understanding the epidemiology, clinical features and pathophysiology of this increasingly diagnosed disease [4–7]. Takotsubo-like cardiomyopathy associated with pheochromocytoma (TTC-pheo) is a recognized but uncommon occurrence with increasing number of published case reports in recent years. Hence we decided to review literature to examine the similarities and differences between primary TTC (TTC-p) and TTC-pheo.

2. Materials and methods

A computer-assisted search of the electronic databases MEDLINE (1966–January 2011), SCOPUS (1965–January 2011) and Google scholar (Advanced Google search) was conducted. All languages were searched, and where necessary, the help of

☆ Franz H. Messerli, MD has been an ad hoc consultant/speaker for the following organizations: Abbott, GSK, Novartis, Pfizer, AstraZeneca, Bayer, Boehringer Ingelheim, Forest, Sankyo, and Sanofi. Vikram Agarwal, MD, MPH has no conflicts of interest. Gunjan Kant, MD has no conflicts of interest. Nidhi Hans, MD has no conflicts of interest.

* Corresponding author at: St. Luke's-Roosevelt Hospital Center, 1000 Tenth Avenue, New York, New York 10019, United States. Tel.: +1 212 523 7373; fax: +1 212 523 7765.
E-mail address: messerli.f@gmail.com (F.H. Messerli).

0167-5273/$ – see front matter
doi:10.1016/j.ijcard.2011.03.027

professional translators was sought. References were also checked for relevant articles, including review papers. The main search terms were: "Takotsubo cardiomyopathy", "Takotsubo syndrome", "stress cardiomyopathy", "stress induced cardiomyopathy", "apical ballooning syndrome", "takotsubo like cardiomyopathy", "takotsubo-like left ventricular dysfunction", "catecholamines", and "pheochromocytoma". All published case reports and abstracts which reported TTC-pheo were chosen. We excluded studies in which the wall motion abnormalities secondary to catecholamine release from the pheochromocytoma were only suggestive of global hypokinesia without associated segmental wall motion abnormalities. Of the reviewed cases, 3 cases obtained from a single letter to the editor, were excluded because of incomplete information [8]. Study selection process is outlined in Fig. 1.

We identified 38 patients from 38 published case reports based on the above search criteria (Table 1) [9–46]. We compared the baseline demographic characteristics, clinical features at presentation, EKG changes, left ventricular ejection fraction (EF), cardiac enzymes and catecholamine levels, and major clinical complications of these patients, to a recently published study by Gianni et al, which examined TTC-p data from 14 previously published case series of TTC [47]. We also compared the signs and symptoms at presentation of our cohort to a large multicentric retrospective study of patients with pheochromocytoma [48]. Data analysis was performed using SPSS version 18. Continuous variables are presented as means ± standard deviations and categorical data as absolute values and percentages. Chi-square test or Fisher's exact test was used as appropriate to compare categorical data, and 2-tailed unpaired Student's t test was used for continuous variables. A 2-sided $p<0.05$ was considered statistically significant.

3. Results

3.1. Overall cohort

The overall features of TTC-pheo and their comparison with TTC-p are presented in Table 2. The majority of patients 27 (71.1%) were women and the overall mean age was 50.3 years, ranging from 17 to 86 years. As compared to the TTC-p patients, TTC-pheo patients were significantly younger, and although women continue to be the majority, the percentage of men in our cohort was significantly higher. As expected, the most common initial presentation was chest pain in 22 (57.9%) patients which mimicked an acute myocardial infarction presentation. This was followed by other classical features of pheochromocytoma including, hypertension (52.6%), palpitation (31.6%), headache (28.9%), and diaphoresis (26.3%). When compared with the study examining the features of pheochromocytoma [48], all these findings were significantly lower in our study (Fig. 2). While 65.7% of patients in the TTC-p review had an identifiable antecedent stressor, only 28.9% of TTC-pheo patients had an antecedent stressor, with 18.4% patients experiencing physical stress, including medical stressors like surgery, and 10.5% patients experiencing emotional stressors. 47.4 % of TTC-pheo patients had a past medical history significant for hypertension; while 13.2% had another episode of TTC diagnosed in addition to the index episode.

The EKG findings in patients with TTC-pheo are similar to the EKG findings of TTC-p, with ST-segment elevation (39.5%) being the most common abnormality, followed by T-wave abnormalities (36.8%), and ST-segment depression (34.2%) (Table 2). Of the T-wave abnormalities, T-wave inversion was present in 28.3%, tall T waves in 5.3% and non-specific T-wave abnormality was present in 2.6% of patients. Of the reported 36 patients, 34 (93.1%) had positive cardiac biomarkers while all 34 patients with reported catecholamine values had elevated levels, compared to 82.7% and 74.3% of patients with TTC-p. At the time of presentation the mean left ventricular EF in the TTC-pheo patients was 28.7%, significantly lower than the TTC-p patients.

Labile blood pressure classically associated with pheochromocytoma, was reported in only 26.3% of patients. Heart failure and cardiogenic shock were reported in 46.7% and 34.2% of TTC-pheo patients respectively, which were significantly higher than in TTC-p patients. Other reported complications include, arrhythmias (7.9%), acute renal failure (7.9%), apical thrombus formation (5.3%), embolism (2.6%), and left ventricular outflow tract obstruction (2.6%). At the time of excision, 21.1% of patients were found to have hemorrhagic necrosis of the pheochromocytoma. 30.3% of patients required treatment with pressors while 13.2% required intra-aortic balloon pump (IABP) support. The overall prognosis of patients was good with majority of them recovering completely, and the mean EF improved to 61.8%. The mortality rate amongst the reviewed patients was 5.3%.

3.2. Apical vs. inverted patterns of stress cardiomyopathy due to pheochromocytoma

Of the reviewed cases, 23 (60.5%) presented with the regular apical TTC-pheo, 12 (31.5%) with inverted TTC-pheo, 2 (5.3%) which did not fit into either, and 1 (2.6%) with no mention of specific pattern of involvement (Table 3). The apical pattern, as compared to the inverse pattern, had a comparatively higher prevalence in women (73.9% vs. 58.3%, $p=0.32$) and affected a comparatively older population (54.3 vs. 43.9, $p=0.09$). Patients developing the regular pattern had greater percentage of past medical history of hypertension (56.5% vs. 25%, $p=0.15$). On EKG the apical pattern had a much higher percentage of patients with ST-segment elevation (56.5% vs. 8.3%, $p=0.01$), T-wave

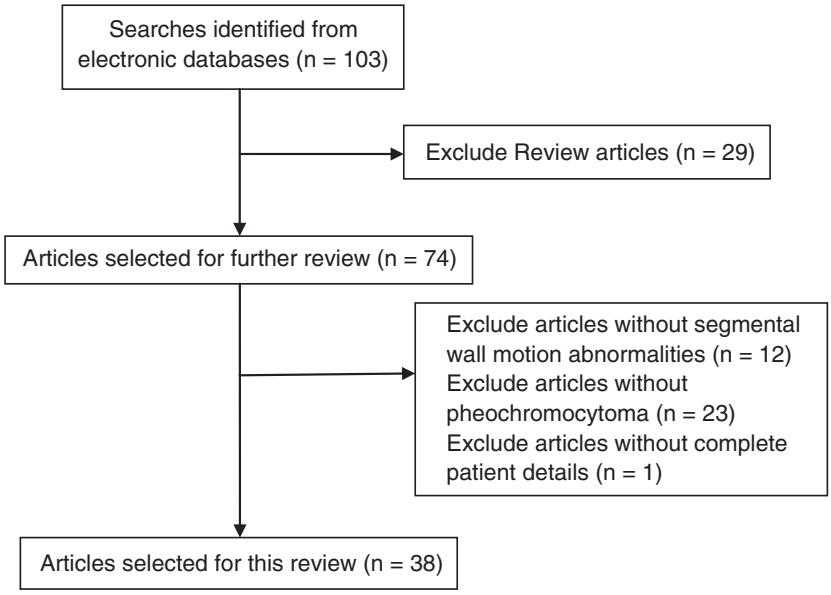

Fig. 1. Study selection process.