

Familial Tako-tsubo Cardiomyopathy: Clinical and Echocardiographic Features Including Magnetic Resonance Imaging Findings

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ABSTRACT

Introduction: Tako-tsubo cardiomyopathy (TCM) is being recognized more frequently; and a familial form of this diagnosis has been suspected but is less well-established.

Case: A 75-year-old patient with a family history of TCM was admitted with suspected ST-segment elevation myocardial infarction. Transthoracic echocardiography showed apical dyskinesia with hyperdynamic basal walls and a left ventricular ejection fraction (LVEF) of 25%. Repeat echocardiography showed normal LVEF of 60% ejection fraction. Cardiac catheterization showed no significant stenosis.

Discussion: TCM is characterized by transient systolic left ventricular dysfunction. A few cases of familial TCM have been reported in the literature and a genetic component is suspected.

Conclusions: Although there has been a paucity of data, familial cases of TCM have been reported. This case study addresses TCM and the familial occurrence of the syndrome, which may have a genetic basis.

and an estimated left ventricular ejection fraction (LVEF) of 25%. Emergent cardiac catheterization was performed and revealed nonsignificant lesions in the coronary vasculature that did not require any intervention. There was mild “myocardial bridging” of 1 vessel. Of note, the ECG abnormalities were extensive and could not be explained by her angiogram. Soon after cardiac catheterization, the patient developed cardiogenic shock and an intra-aortic balloon pump (IABP) was needed to stabilize her hemodynamics. Biochemistries showed a troponin T peak of 0.86 ng/ml and a brain natriuretic peptide of 144pg/ml (N < 125 pg/ml).

CASE REPORT

A 75-year-old white woman presented to the Emergency Department with acute onset of chest pain. There were no precipitating events prior to her presentation. She had a family history of Tako-tsubo cardiomyopathy (TCM) in her older sister, who had experienced emotional stress prior to her admission. The patient’s 12-lead electrocardiogram (ECG) demonstrated transmural myocardial ischemia with 2 mm ST elevations in the anterior leads V2-V6 (Figure 1). Transthoracic echocardiography (TTE) revealed apical dyskinesia “apical ballooning,” with hyperdynamic basal walls

On magnetic resonance imaging (MRI) scan using gadolinium, there was delayed enhancement in the anterior wall (Figure 2). In the ensuing hospital days, her clinical condition improved dramatically. Repeat TTE done 4 days later showed that the LVEF had improved to 43%, while another study repeated 6 months post discharge showed an ejection fraction to 63% with complete resolution of the apical wall motion abnormalities.

The initial clinical presentation suggested an acute coronary syndrome; however, diagnostic workup showing transient ECG abnormalities, echocardiographic findings of apical dyskinesia, cardiogenic shock, and no significant lesions in coronary arteries raised a suspicion for possible TCM. Additionally, the improvement of the ECG and echocardiographic findings led us to believe that this was most likely a case of TCM.

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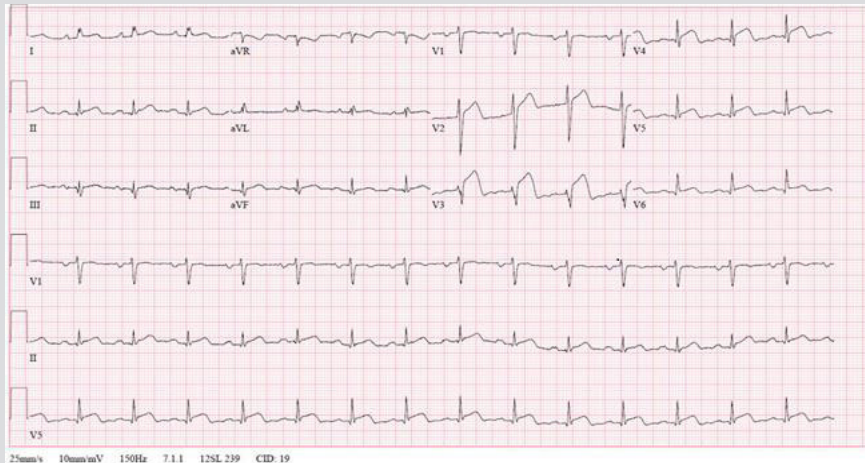
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BACKGROUND AND DISCUSSION

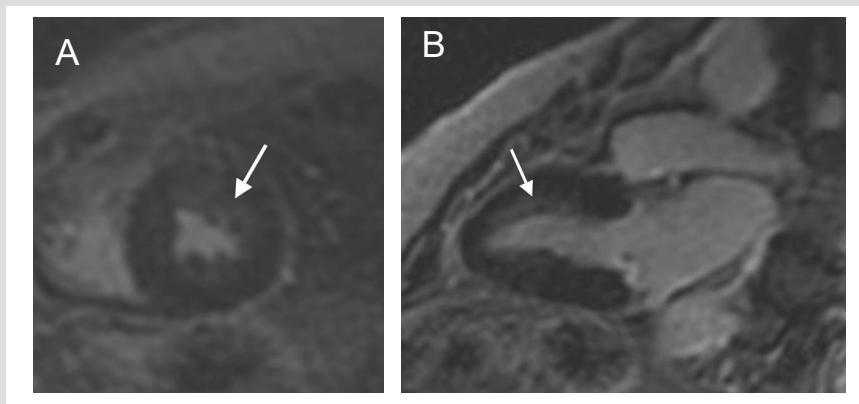
TCM is being recognized more frequently, and while there has been speculation about a familial form of this disease, it is less well-established. Echocardiographic findings typically show apical dyskinesia “ballooning” of the left ventricle in systole. The shape resembles that of a fisherman’s pot used

Figure 1. 12-lead ECG on Admission Showing ST Elevations in Leads V2-V6 Consistent With Transmural Myocardial Ischemia



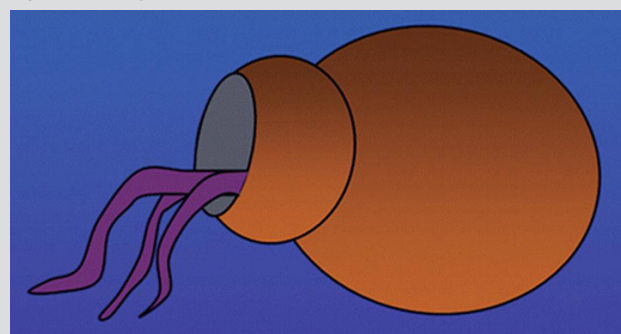
Abbreviation: ECG, electrocardiogram.

Figure 2. Cardiac MRI Scans Using Gadolinium Enhancement



A. Short axis view of magnetic resonance imaging showing area of delayed gadolinium enhancement in anterior wall (see arrow). **B.** Long axis view showing area of delayed enhancement in left ventricle anterior wall (see arrow).

Figure 3. Fishing Pot used to Catch Octopi in Japan



Pot has narrow neck and wide base to prevent octopus from escaping once it enters the pot.

in Japan to catch octopi. The pot, referred to as "takotsubo", has a round base and a narrow neck (Figure 3). The echocardiographic wall motion abnormalities are reversible and usually resolve within 4 to 8 weeks of the acute event. The MRI findings in this condition may be helpful if echocar-

diographic images are suboptimal or if ischemic heart disease is present at the same time.¹⁻⁴

This report illustrates a case of TCM and the echocardiographic and MRI findings in a patient whose sister was diagnosed 3 years earlier with the same condition.

A PUBMED and Google Scholar search was performed using specific keywords to identify cases of familial TCM. It is sometimes also called "apical ballooning syndrome" or "stress cardiomyopathy" and represents a reversible form of cardiomyopathy that commonly presents in association with acute emotional or physiologic stressful conditions.⁵ The clinical presentation is similar to an acute coronary syndrome in the absence of obstructive coronary artery disease and does not explain the distribution of associated transient wall motion abnormalities.⁶ Postmenopausal women seem particularly prone for unclear reasons. The protective role of estrogen hypothesis has been raised in the past.⁷ However, the mechanism by which a lack of estrogen predisposes to the condition is not well understood. The pathophysiology of the syndrome is

unknown but may involve pathologic sympathetic myocardial stimulation caused by a surge in plasma catecholamines.⁸ In addition, metabolic disturbances and dysfunction of microcirculation also are suspected to be the underlying mechanisms.⁹

Typically, patients present with chest pain and shortness of breath, transient electrocardiographic changes, moderate troponin elevation (median initial troponin 7 to 8 times upper limits of normal). Echocardiography initially shows regional wall motion abnormalities. These regional abnormalities are mostly confined to the apical and midventricular walls (with preserved basal segment systolic function) and usually resolve within 4 to 8 weeks of the acute event. Coronary angiography typically shows normal coronary arteries or nonsignificant lesions. The prognosis is, perhaps, not as benign as was previously thought. Data from the United States Medicare database (2007-2012) shows that 30-day and 1-year mortality rates vary from 2.5% to 6.9% and 4.7% to 11.7%, respectively.¹⁰

According to a review by Gianni et al,¹¹ the true prevalence of TCM remains uncertain, but a reasonable estimate of its incidence is approximately 2% of all patients presenting with an acute coronary syndrome. Their data also showed an inhospital mortality of 1.1%; only 3.5% of patients experience a recurrence.¹²

A familial form of TCM has been suspected and is reported in the literature.¹³⁻¹⁹ PUBMED and Google Scholar searches revealed a few familial cases of TCM in the last 15 years (Table). These reports confirm that TCM can be seen in family members, suggesting a possible genetic etiology of this condition. Our case report also provides evidence that this condition can be encountered in family members. The patient's older sister suffered similar complaints and was diagnosed elsewhere with TCM; her clinical presentation was identical to our patient and her cardiac catheterization demonstrated normal coronary arteries. Additionally, echocardiography showed complete resolution of her LVEF and normalization of apical wall motion abnormalities at 4 weeks after the acute event.

A 2014 study of 28 TCM patients performed a whole-exome sequencing of genes related to catecholamine and adrenergic signaling, revealing that 93% of the patients had at least a malignant variant of 55 candidate genes.²⁰

A 2017 genome-wide association study of 95 patients with TCM revealed 68 loci of potential nucleotide polymorphism. Eighteen out of 65 loci contained single nucleotide polymorphism (SNP) supported by SNPs in high linkage disequilibrium.²¹

The genetics of TCM still remain unclear. Hence, high-quality phenotyping and identification of candidate genes is necessary to further explore and understand the pathogenesis of TCM.

In regard to MRI in TCM, there are isolated publications describing small diffuse areas of late enhancement in the anterior and apical segments.¹⁻⁴ The edema on T2 weighted images is typically located in the apical mid ventricular planes, sparing the base plane. However, myocardial edema also is seen in acute myocardial infarction and myocarditis. Late gadolinium enhancement (LGE) in MRI is generally absent in TCM as opposed to myocardial infarction, where it is very intense (more than 5 SD above the mean signal intensity of the remote myocardium). However, it can be seen occasionally in TCM. LGE may help differentiate TCM from myocarditis, where a "patchy" distribution of myocardial edema is seen.²²

Table. Cases of Familial Tako-tsubo Cardiomyopathy and Precipitating Factors Triggering Clinical Events

Author	Familial Relationship	Precipitating Factors
Pison ¹⁷ (2004)	Sisters	Argument with husband, physical exercise
Kumar ¹³ (2010)	Mother-daughter	Severe emotional stress
Subban ¹⁴ (2012)	Mother-daughter	Emotional stress after sudden death of a family member
Sharkey ¹² (2013)	Mother-daughter	Stressful event
Masumeci ¹⁹ (2013)	Sisters	Emotional stress after sudden death of a family member
Ikutomi ¹⁰ (2014)	Sisters	Stress
Caretta ¹⁸ (2015)	Sisters	Skin prick test for asthma, emotional stress after a dispute

CONCLUSIONS

Multiple familial cases of TCM have been reported, although there has been a paucity of data regarding case series. The search for a genetic basis of the disease is ongoing, and genetic testing is not currently available commercially. In TCM, characteristic transient wall motion abnormalities are seen by echocardiography. The ECG changes are generally overwhelming, resembling an acute coronary syndrome, and angiographic findings are essentially normal. Coronary angiography is mandatory in the diagnosis of TCM. MRI findings are generally nonspecific but may be useful in differentiating from ischemic heart disease and myocarditis. At this time, MRI is not performed routinely in patients with suspected TCM. The recurrence rate of TCM is thought to be around 3.5%.¹² Awareness of the condition is key to explaining the clinical presentation, although treatment is similar to patients presenting with acute coronary syndromes.

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REFERENCES

- Gerbaud E, Montaudon M, Leroux L, et al. MRI for the diagnosis of left ventricular apical ballooning syndrome. *Eur Radiol.* 2008 May;18(5):947-954. doi:10.1007/s00330-008-0853-9.
- Assomull RG, Lyne VC, Keenan N, et al. The role of cardiovascular magnetic resonance in patients presenting with chest pain, raised troponin, and unobstructed coronary arteries. *Eur Heart J.* (10):1242-1249. doi:10.1093/eurheartj/ehm113.
- Mitchell J, Hadden T, Wilson JM, Achari A, Muthupillai R, Flamm S. Clinical features and usefulness of cardiac magnetic resonance imaging in assessing myocardial visibility and prognosis in Tako-tsubo cardiomyopathy. *Am J Cardiol.* 2007;100(2):296-301. doi:10.1016/j.amjcard.2007.02.091.
- Cummings K, Bhalla S, Jaridan-Nejac C, Bierhals A, Gutierrez F, Woodard P. A pattern-based approach to assessment of delayed enhancement in non-ischemic cardiomyopathy at MR imaging. *Radiographics.* 2009;29(1):89-103. doi: 10.1148/rg.291085052.
- Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or Stress cardiomyopathy): a mimic of acute myocardial infarction. *Am Heart J.* 2008;155(3):408-417. doi:10.1016/j.ahj.2007.11.008.
- Sharma AK, Singh JP, Heist EK. Stress cardiomyopathy: diagnosis, pathophysiology, management and prognosis. *Crit Pathw Cardiol.* 2011;10(3):142-147. doi:10.1097/HPC.0b013e31822f4d37.
- Limongelli G, D'Alessandro R, Masarone D, et al. Takotsubo cardiomyopathy: do genetics matter? *Heart Fail Clin.* 2013;9(2):207-216. ix. doi:10.1016/j.hfc.2012.12.008.

8. Kurisu S, Sato H, Kawagoe T, et al. Tako-tsubo-like left ventricular dysfunction with ST segment elevation: a novel cardiac syndrome mimicking acute myocardial infarction. *Am Heart J.* 2002;143(3):448-455.
9. Handy AD, Prasad A, Olson TM. Investigating genetic variation of adrenergic receptors in familial stress cardiomyopathy (apical ballooning syndrome). *J Cardiol.* 2009;54(3):516-517. doi:10.1016/j.jjcc.2009.08.008.
10. Ikutomi M, Yamasaki M, Matsusita M, et al. Takotsubo cardiomyopathy in siblings *Heart Vessels.* 2014;29(1):119-122. doi:10.1007/s00380-013-0345-y. Epub 2013 Apr 7.
11. Gianni M, Dentali F, Grandi AM, Sumner G, Hiralal R, Lonn E. Apical ballooning syndrome or takotsubo cardiomyopathy: a systemic review. *Eur Heart J.* 2006;27(13):1523-1529.
12. Sharkey SW, Lips DL, Pink VR, Maron BJ. Daughter-mother tako-tsubo cardiomyopathy. *Am J Cardiol.* 2013;112(1):137-138. doi:10.1016/j.amjcard.2013.02.063. Epub 2013 Apr 2.
13. Kumar G, Holmes DR Jr, Prasad A. Familial apical ballooning syndrome (Takotsubo cardiomyopathy). *Int. J Cardiol.* 2010 Oct 29;144(3):444-445. doi:10.1016/j.ijcard.2009.03.078.
14. Subban V, Ramachandran S, Victor SM, Gnanaraj A, Ajit MS. Apical ballooning syndrome in first degree relatives. *Indian Heart J.* 2012;64(6):607-609. doi:10.1016/j.ihj.2012.07.004.
15. Kapoor D, Bybee KA. Stress cardiomyopathy syndrome: a contemporary review. *Curr Heart Fail Rep.* 2009;6(4):265-271.
16. Fernández-Pérez GC, Aguilar-Arjona JA, de la Fuente GT, Samartín M, Ghioldi A, Arias JC, Sánchez-González J. Takotsubo cardiomyopathy: assessment with cardiac MRI. *AJR Am J Roentgenol.* 2010 Aug;195(2):W139-145. doi:10.2214/AJR.09.3369.
17. Pison, L, De Vusser P, Mullens W. Apical ballooning in relatives. *Heart.* 2004; 90(12), e67. <http://doi.org/10.1136/hrt.2004.046813>.
18. Caretta G, Robba D, Vizzardi E, Bonadei I, Raddino R, Metra M. Tako-tsubo cardiomyopathy in two sisters: a chance finding or familial predisposition? *Clin Res Cardiol.* 2015;104(7):614-616. doi:10.1007/s00392-015-0837-0. Epub 2015 Mar 6.
19. Musumeci B, Saponaro A, Pagannone E, et al. Simultaneous Takotsubo syndrome in two sisters. *Int J Cardiol.* 2013;165(3):e49-50. doi:10.1016/j.ijcard.2012.11.016. Epub 2012 Nov 22.
20. Goodloe AH, Evans JM, Middha S, Prasad A, Olson TM. Characterizing genetic variation of adrenergic signalling pathways in Takotsubo (stress) cardiomyopathy exomes. *Eur J Heart Fail.* 2014;16(9):942-949. doi:10.1002/ehf.145.
21. Eitel I, Moeller C, Munz M, et al. Genome-wide association study in takotsubo syndrome — Preliminary results and future directions. *Int J Cardiol.* 2017;236:335-339. doi:10.1016/j.ijcard.2017.01.093.
22. Eitel L, von Knobelsdorff-Brenkenhoff F, Bernhardt P, et al. Clinical characteristics and cardiovascular magnetic resonance findings in stress (takotsubo) cardiomyopathy. *JAMA.* 2011;306(3):277-286. doi:10.1001/jama.2011.992.13. Subban V, Ramachandran S, Victor SM, Gnanaraj A, Ajit MS. Apical ballooning syndrome in first degree relatives. *Indian Heart J.* 2012;64(6):607-609. doi:10.1016/j.ihj.2012.07.004.

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