Revista Mexicana de
Cardiología
Vol. 27 No. 3
July-September 2016

CLINICAL CASE

Takotsubo syndrome associated with myasthenic crisis. A case report

Síndrome de takotsubo asociado a crisis miasténica. Presentación de un caso

Héctor Hugo Escutia Cuevas,* Roberto Domínguez López,**
Benjamín Padilla Trejo,*** Rosa Rebeca Vargas Ramón,****
Héctor Emilio Montes Isunza,* Myrlene Rodríguez Brito*****

Key words:
Myasthenia gravis, myastenic crisis, takotsubo, cardiomyopathy, broken heart.

Palabras clave:
Miastenia grave, crisis miasténica, takotsubo, cardiomiopatía, corazón roto.

* División de Cardiología, Centro Médico Nacional 20 de Noviembre, ISSSTE.
** Cardiología Intervencionista, Centro de Alta Especialidad «Dr. Rafael Lucio», SSA.
*** Neurología, Centro de Alta Especialidad «Dr. Rafael Lucio», SSA.
**** Medicina Interna, Centro de Alta Especialidad «Dr. Rafael Lucio», SSA.
***** Cirugía Cardiotorácica, Instituto Nacional de Cardiología «Ignacio Chávez», SSA.

Received:
30/05/2016
Accepted:
29/08/2016

ABSTRACT

Introduction: The takotsubo syndrome is a rare clinical entity commonly associated with elderly women (ratio 6:1), easily confused with an acute ischemic syndrome, strangely associated with a myasthenic crisis. It is characterized with chest pain, elevated biomarkers, ST segment elevation, absence of coronary flow obstruction, and a characteristic deformity (anteroapical dyskinesia) of the left ventricle; these changes associated with a stressor. **Case report:** A woman of 69 years, diagnosed with myasthenia gravis six years ago, who entered in the intensive care unit with a suspected diagnosis of acute coronary syndrome and respiratory failure which required mechanical ventilation. Coronary angiography discarded a coronary disease. Ventriculography revealed a systolic anteroapical deformation. Treatment was initiated with acetylcholinesterase inhibitors and plasmapheresis with partial response, it required the use of vasoactive amines, with a suitable progressive cardiovascular and neurological outcome, with echocardiographic resolution. **Conclusions:** The takotsubo syndrome can be associated with myasthenia gravis and myasthenic crisis. The prognosis depends on early diagnosis, appropriate differential diagnosis, immediate treatment of myasthenic crisis, and management of the hemodynamic consequences of the takotsubo syndrome.

RESUMEN

Introducción: *El síndrome de takotsubo es una entidad clínica poco frecuente asociada comúnmente con las mujeres de edad avanzada (relación 6:1), puede fácilmente confundirse con un síndrome isquémico agudo, extrañamente asociado con una crisis miasténica. Se caracteriza por dolor torácico, biomarcadores elevados, elevación del segmento ST, ausencia de obstrucción del flujo coronario, y una deformidad característica (discinesia anteroapical) del ventrículo izquierdo; estos cambios asociados con un factor de estrés.* ***Caso clínico:*** *Una mujer de 69 años, con diagnóstico de miastenia gravis hace seis años, que ingresó en la Unidad de Cuidados Intensivos con un diagnóstico de sospecha de síndrome coronario agudo e insuficiencia respiratoria que requirió de ventilación mecánica. La angiografía descartó una enfermedad coronaria. La ventriculografía reveló una deformación anteroapical sistólica. Se inició el tratamiento con inhibidores de la acetilcolinesterasa y plasmaféresis con respuesta parcial, se requirió el uso de aminas vasoactivas, con un resultado progresivo cardiovascular y neurológico adecuado, con resolución ecocardiográfica.* ***Conclusiones:*** *El síndrome de takotsubo puede estar asociada con miastenia gravis y la crisis miasténica. El pronóstico depende del diagnóstico precoz, el diagnóstico diferencial adecuado, el tratamiento inmediato de la crisis miasténica, y la gestión de las consecuencias hemodinámicas del síndrome takotsubo.*

INTRODUCTION

The takotsubo syndrome (TKS), takotsubo cardiomyopathy, stress cardiomyopathy, or broken heart syndrome; is a rare disease in Mexico, poorly documented in our country, in the first instance confused with acute coronary syndrome. It is necessary to make immediate distinction based on the differential diagnosis because their medical management is largely different of an acute myocardial infarction. The pathognomonic feature of TKS is the reversible systolic left ventricular deformation as a result of anteroapical dyskinesia or hypokinesia

Institución en la que se realizó el trabajo: Centro de Alta Especialidad «Dr. Rafael Lucio»; Xalapa, Veracruz.

coupled with compensatory hyperkinesis of the basal segments of the ventricle. The TKS is more prevalent in women (6:1) middle-aged and older, and its onset before 50 years old is exceptional.

Concerning on the myasthenia gravis on the adult, in most cases it is an acquired autoimmune disorder, caused by the formation of antibodies against acetylcholine receptors, tyrosine muscle specific kinase (Musk), or LRP4.[1] Clinically, myasthenia gravis is characterized by focal o generalized muscle weakness exacerbated induced by exercise.[1] In some cases, myasthenia gravis may show a sudden clinical deterioration (myasthenic crisis), if the respiratory muscles are involved it can be caused an acute respiratory failure requiring mechanical ventilatory support. A myasthenic crisis is usually a critical event triggered by physical or emotional stress. Recently, it has shown that such stress reaction can even cause TKS,[2] the joint presentation of these diseases has been described in counted neuro-critical patients. The case reported here shows an example of TKS associated with myasthenic crisis.

CASE REPORT

Woman of 69 years old, resident of Xalapa, Veracruz; housewife, smoking and alcoholism negative. History of hypertension diagnosed 20 years ago and treated with losartan 50 mg twice a day. Myasthenia gravis diagnosed 6 years ago at the National Institute of Neurology and Neurosurgery, in outpatient follow-up in that hospital; chronic treatment with pyridostigmine 60 mg every 6 hours. She began her symptoms 45 days before the hospitalization with the presence of muscle weakness in pelvic and thoracic limbs no compromising the ambulation but difficulting her daily activities, seven days after was added progressive swallowing compromise initially for masticating and then to swallow solids pregressing to liquids, the reason why he stopped her oral treatment. Twelve hours after discontinuation of oral treatment was added a rapidly progressing dyspnea to grade IV New York Heart Association (NYHA), being brought to the emergency room High Specialty Centre «Dr. Rafael Lucio», in which the diagnosis of myasthenic crisis is made and specific treatment was started with intravenous neostigmine 4 mg single dose as well as plasmapheresis during 4 daily sessions with a total of 4 plasma exchanges with 60 grams of 20% albumin each, with immediate improvement of symptoms. For the next 7 days of her hospitalization had fluctuations in muscle strength and swallowing, pyridostigmine 60 mg every 4 hours was initiated, no achieving a complete improvement of symptoms. Three days later she began with dyspnea at rest and chest pain, being admitted to the intensive care unit of the hospital. Upon arrival respiratory failure was documented so we decided to perform endotracheal intubation and mechanical ventilatory support was initiated. Electrocardiogram and cardiac biomarkers were performed, and based on them an acute coronary syndrome (ST-segment elevation myocardial infarction) is suspected, it was added in the management clopidogrel 600 mg single dose, acetylsalicylic acid 300 mg load, low molecular weight heparin, anticoagulant and atorvastatin 80 mg in single dose; coronary angiography was performed at 10 hours of pain symptoms began, reporting the study without significant coronary lesions and normal flow of all epicardial arteries and morphologic and mobility ventricular abnormalities compatible with takotsubo syndrome. Treatment was started with bisoprolol 2.5 mg every 24 hours and enalapril 5 mg every 12 hours, continuing treatment until the discharge. Orotracheal extubation was achieved within 5 days and vasoactive amines were removed 24 hours later, and being discharged 5 days later, cardiovascularly stable to continue ambulatory follow-up.

Physical examination on admission: blood pressure 100/70 mmHg, heart rate 110/min, respiratory rate 28/min, temperature 36.5 ºC, weight 65 kg, height 1.55 mt, body mass index 27.08 kg/m2. Alert and oriented, with superior mental functions of attention, memory, praxis, gnosis with no changes, nonassessable speech; bilateral ptosis increases with fatigue tests (elevation look at a fixed point, repeated blinking), positive sign of fallen eyelid and vertical diplopia, without meningeal signs, surface and nociceptive sensitivity preserved, muscle strength in the upper extremities 4/5 and lower 5/5, muscle stretch reflexes ++ / ++++ distal

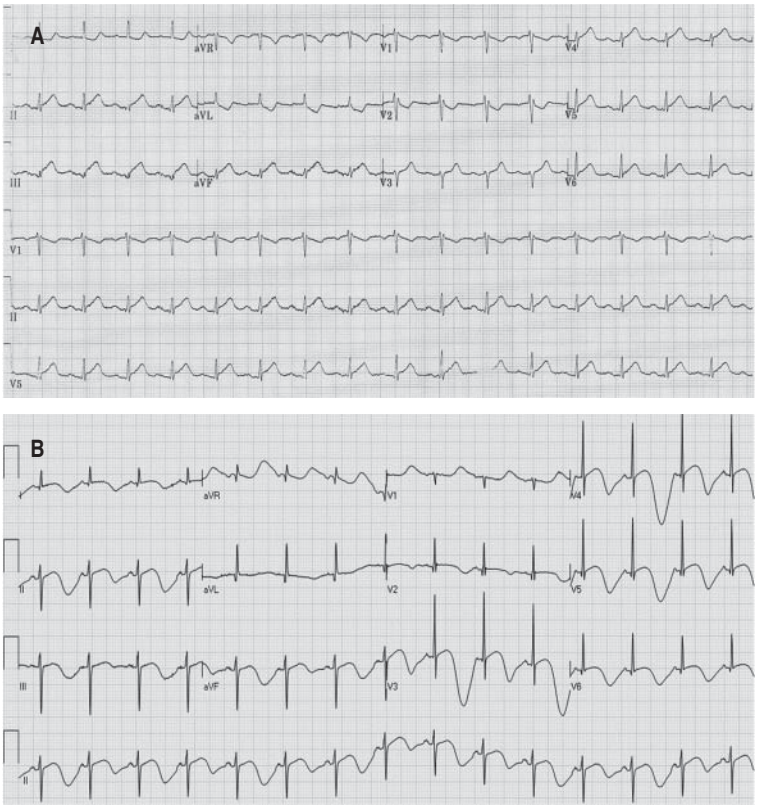

Figure 1. A 12-lead electrocardiogram in sinus rhythm with heart rate of 100 beats per minute, ST segment elevation of 0.2 mV in DII, DIII, aVF and V4-V6, suggestive of inferolateral acute ST segment elevation myocardial infarction (**A**). Electrocardiographic monitoring after 48 hours with presence of deep T wave inversion and asymmetric branches in DII, DIII, aVF and V3-V6 (**B**).

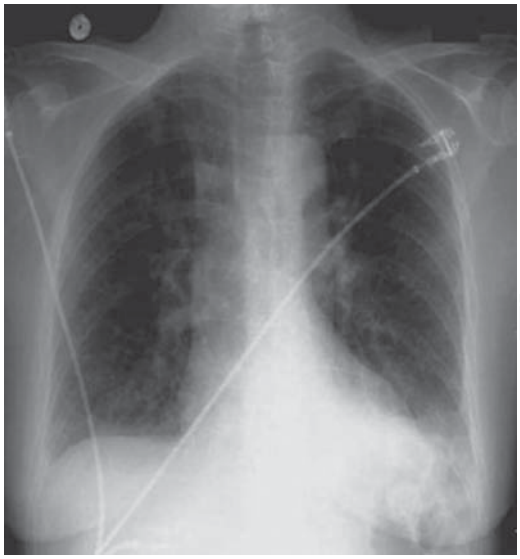

Figure 2.

Chest X-ray in anteroposterior projection with increased bilateral vascular pattern, without apparent cardiomegaly, no other visible changes.

and proximal, without relaxation of sphincters, march nonassessable. Pupils with normal and symmetrical movements and reflexes, normal fundus, hydrated oral mucosa; neck without jugular ingurgitation, without lymphadenopathy. Normal and symmetrical chest movements, normal breath sounds, normal voice transmission and vocal vibrations; rhythmic heart sounds with diminished intensity and frequency, bright S1, S2 with physiological splitting, no audible S3, S4 or murmurs. Abdomen flat, soft and depressible, normal peristalsis without organ enlargement, tympanic to percussion. Lower extremities without edema, immediate capillary refill, peripheral pulses were present and normal.

Results of laboratory studies: hemoglobin 17.5 g/dL, hematocrit 52.2%, neutrophils 8,350/mm3, lymphocytes 840/mm3, monocytes 50/mm3, glucose 122 mg/dL, creatinine 0.77 mg/dL, urea 32.1 mg/dL, sodium 146 mmol/L, chloride 116 mmol/L, calcium 8.9 mg/dL, total bilirubin 1.2 mg/dL, AST 32 U/L, ALT 15 U/L, TSH 1.71 ug/dL, T4 7.38 ug/dL, T3 total 0.47 ug/IU. Urine metanephrine 0.63 mg/day, normetanephrine 498 nmol/day, dopamine 982 µg/day, adrenaline 36 µg/day, noradrenaline 99 µg/day. Plasmatic catecholamines: noradrenaline 832 ng/mL, adrenaline 316 ng/mL. Biomarkers curve: troponin I: 0.67/0.59/0.29/0.06 µg/L, CK-Mb: 72/63/32/23 U/L. Electrocardiogram: sinus rhythm with heart rate of 100 beats per minute, ST segment elevation of 0.2 mV in DII, DIII, aVF and V4-V6. Control of 48 hours with presence of deep T wave inversion and asymmetric branches in DII, DIII, aVF and V3-V6 *(Figure 1)*. Chest X-ray in anteroposterior projection with increased bilateral vascular pattern, without apparent cardiomegaly *(Figure 2)*.

Coronary angiogram: selective femoral system with 6 French (Fr) JL and JR catheters, observed: left main coronary system bifurcated, anterior descending artery Gensini type III, without significant lesions, and TIMI III distal flow. Circumflex without significant lesions, normal distal flow. Right coronary artery dominant, without significant coronary lesions, normal distal flow *(Figure 3)*. Ventriculography observed basal hyperkinesis with anteroapical and inferoapical hypokinesia *(Figure 4)*. Echo-

cardiogram: transthoracic study after 3 months of follow-up, with left ventricle of normal size, without alteration in partial or segmental mobility, ejection fraction of 76%, without valvular disease, systolic pressure in the pulmonary artery 22 mmHg, the rest with no alterations *(Figure 5)*.

DISCUSSION

The TSK is a clinical entity described in 1990 by Sato, et al; who described the first cases characterized by acute anginal chest pain in the absence of angiographic coronary obstruction and apical systolic heart characteristic deformation.[3] The TKS owes its name to the Japanese technique of fishing for octopus (tako: octopus, tsubo: pot) in pots, whose forms recall the left ventricle in systole during the acute phase of the syndrome. The TKS as a clinical entity was considered in 2001, with the study of Tsuchihashi, et al; who published a retrospective analysis of 88 patients with a syndrome characterized by chest pain, initially identical electrocardiographic changes of acute myocardial infarction, elevated cardiac biomarkers, coronary arteries without significant lesions and characteristic apical left ventricular dyskinesia/hypokinesia, that normalize within a few days.[4] In consequent years new cases have been reported in different countries, thus proving that the STK is not restricted to certain geographical areas.

It mainly affects elderly women (over 80% of cases).[4,5] Its pathogenesis is not yet purely determined and is probably multifactorial. Theoretically the acute and intense adrenergic hyperactivity which is due to physical, psychological or both stress, increase serum levels of catecholamines, such sympathetic hyperactivity causes a depression of the contractile function of the left ventricle in the apical region by focused microvascular spasm (neuromyocardic syndrome), with the consequence of morphological cardiac deformation, characteristic of TKS.[5] As observed in the series of Tsuchihashi[4] and in our patient, the TKS was preceded by a stressful event, which supports the hypothesis proposed above; however, there is still no evidence of elevated catecholamines in the myocardium of these patients.[6]

In the original series of Tsuchihashi,[4] only 7% of cases had a neurological factor as a possible trigger, none of the patients reported or associated with myasthenia gravis. In recent years there have been reports of TKS related with myasthenic crisis and other neurological processes such as: subarachnoid hemorrhage,[7] stroke,[8] Guillain-Barré syndrome[9] and convulsive crisis.[10] In all of them the stress is related as a trigger.

Counting our case, there have been reported a total of eleven cases of TKS in patients with myastenic crisis.[11-20] Their characteristics

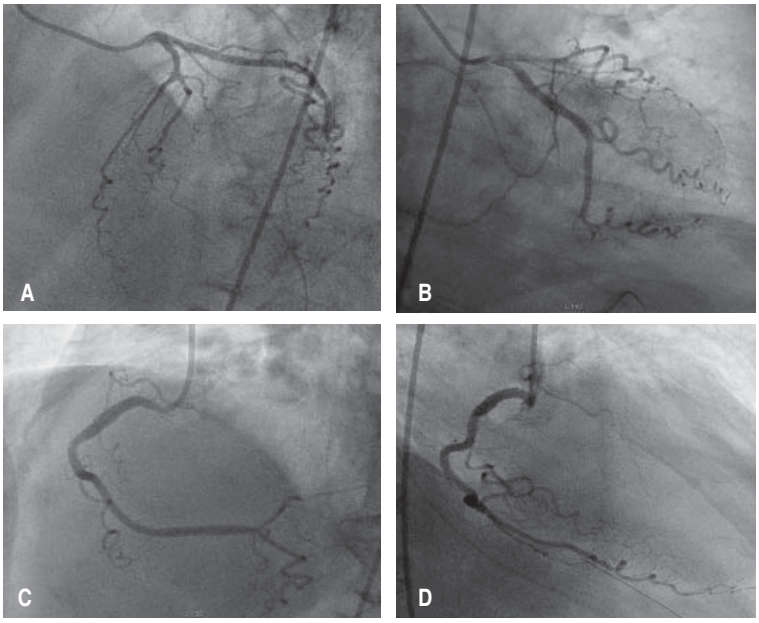

Figure 3. Diagnostic coronary angiogram, which is reported without significant angiographic lesions with normal distal flow in both the left system **(A** and **B)** and right coronary system **(C** and **D).**

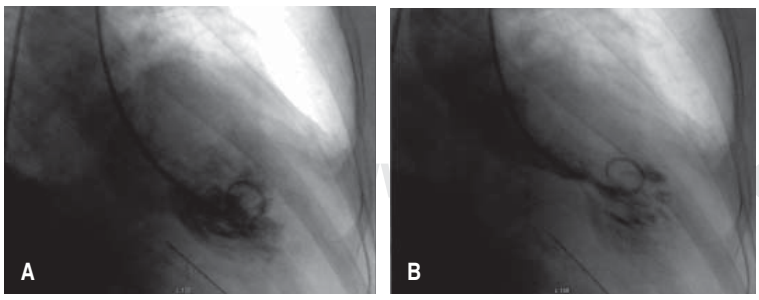

Figure 4. Left ventriculography in right anterior oblique projection in which the characteristic deformation of STK in diastole **(A)** and more pronounced in systole **(B)** is observed.

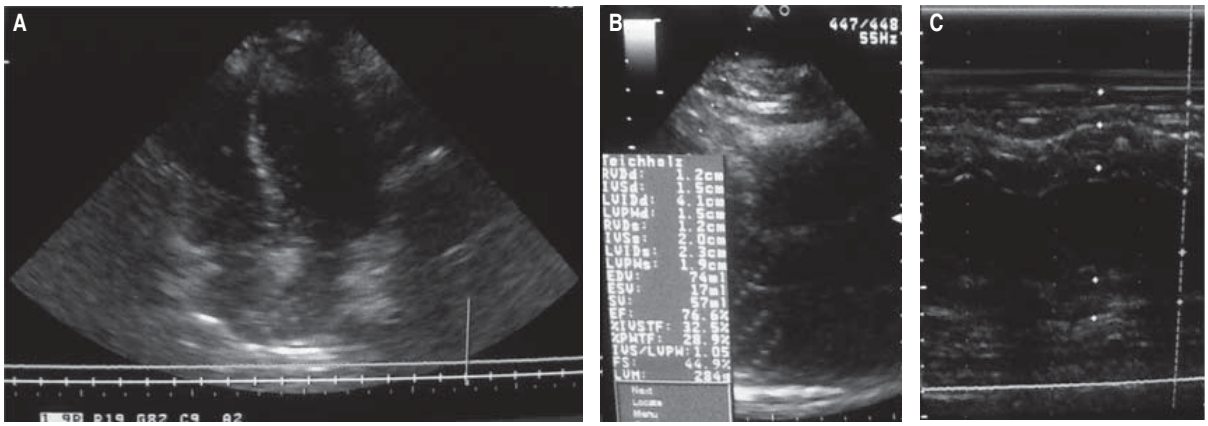

Figure 5. Transthoracic echocardiogram of three months after discharge, in 4-chamber axis projection, the left ventricle shows no alterations in morphology during relaxation **(A)**, without chamber enlargement, left ventricular ejection fraction preserved displayed by Teichholz **(B)**, and adequate ventricular mobility by M mode **(C)**.

are summarized in *table I*. In two of them can be attributed a potential responsible role to the plasmapheresis.[19,20] Although the limited temporal relationship between the development of TKS and myasthenic crisis in the absence of another therapeutic factor, allows us to provide a greater weight in terms of causality to the stress. Another consideration may be generated from the fact that there is no published case of TKS as an adverse effect of treatment with plasmapheresis.

Including our patient, in ten patients the TKS was presented during the mechanical ventilation support *(Table I)*. In a patient the orotracheal intubation after a seizure during myasthenic crisis was necessary. Ten patients received acetylcholinesterase inhibitors during acute event of TKS, six patients received steroids, two required mycophenolate mofetil, one tacrolimus, three patients were treated with immunoglobulin and four patients with plasmapheresis. Ten patients developed classical TKS with apical dyskinesia and basal segments hyperkinesia, and one patient developed a global TKS with akinesia/hypokinesia of all segments. Four patients received dobutamine, one disopyramide, two diuretics, one lidocaine and two noradrenaline. Nine patients recovered completely of TKS, but in two patients the outcome was fatal, one of the deceased patients developed global type. Only one of the patients had a recurrence of TKS.

A direct pathophysiological association between myasthenic crisis and the TKS is unlikely because in myasthenia gravis the cholinergic deficit occurs in the receptor of the striated skeletal muscle, and the pathophysiological feature more accepted in the secondary TKS to any cause is the hyperadrenergic systemical state, usually mediated by physical or emotional stress.

The stress due to myasthenic crisis can be attributed to respiratory failure and anxiety caused by transient dyspnea. Probably the inducing factor of myasthenic crisis, lead to physical stress and contribute to the development of TKS.

CONCLUSIONS

The TKS must be taken into consideration as a clinical entity without direct pathophysiological relationship with myasthenia gravis and myasthenic crisis. Although the association is rare, it is not known for sure their relationship in clinical practice because of the few existing case reports. The prognosis for these patients, as observed in our clinical case, depends on timely diagnosis, appropriate differential diagnosis, immediate treatment of myasthenic crisis, and with the management of hemodynamic consequences of TKS. The cardiologist needs to know that there may be a correlation between the two

Table I. Myasthenic crisis associated with takotsubo syndrome. Reported cases (until 2016, including our case).

Type of myastenia	Sex	Age	Type of TKS	Treatment of TKS	Treatment of MG	MVA	Outcome	Reference
MG	W	75	Classic	PCM	DSP, CTS	Yes	CR	11
MG	W	50	Classic	DB, DR, FR	NOS, CTS, IGIV	Yes	CR	12
MG	W	83	Classic	NM	DSP, CTS, IGIV	Yes	CR	13
MG	M	77	Classic	ACEI	DSP, PF, CTS, MF	Yes*	CR	14
MG	W	82	Classic	NM	IGIV	Yes	CR	15
MG	W	64	Classic	NM	DSP	Yes	CR	16
MG	W	60	Classic	NM	DSP, MF, PF, CTS	Yes	CR	17
Ocular	W	63	Classic	DR, lidocaine	DSP, CTS	Yes	Death	18
MG	M	64	Global	DB, NE	DSP, PF	Yes	Death	19
MG	W	83	Classic	DB	DSP, PF, TCR	Yes	CR	20
MG	W	69	Classic	DB, BB, ACEI	PF, NOS, DPS	Yes	CR	Escutia, et al.

Abbreviations: MG = myasthenia gravis, TKS = takotsubo syndrome, MVA = mechanical ventilation assistance, DB = dobutamine, DR = diuretics, BB = betablocker, ACEI = angiotensin convertin enzime inhibitor, FR = fluid restriction, NM = not mentioned, NE = norepinephrine, DSP = disopyramide, CTS = corticosteroids, NOS = neostigmin, IGIV = immunoglobulin G, PF = plasmapheresis, MF = mycophenolate mofetil, TCR = tacrolimus, CR = complete recovery, * required intubation during convulsive seizures.

diseases, and it is the duty of neurologist to know the existence of this cardiomyopathy and take it into consideration in all patients with myasthenic crisis and other neurocritical conditions also related.

Acknowledgments

To the Clinical Services of Cardiology, Neurology and Internal Medicine of the High Specialty Centre «Dr. Rafael Lucio» for the professional and cordial support, as well as the facilities loaned by the institution to carry out this work.

REFERENCES

1. Sussman J, Farrugia M, Maddison P, Hill M, Leite MI, Hilton-Jones D. Myasthenia gravis: association of British neurologists' management guidelines. Pract Neurol. 2015; 15: 199-206.
2. Thanaviratananich S, Katirji B, Alshekhlee A. Broken heart syndrome during myasthenic crisis. J Clin Neuromuscul Dis. 2014; 15: 90-95.
3. Sato H, Tateishi H, Uchida T. Takotsubo-type cardiomyopathy due to multivessel spasm. In: Kodama K, Haze K, Hon M, eds. Clinical aspect of myocardial injury: from ischemia to heart failure. Tokyo: Kagakuhyouronsya; 1990: pp. 56-64.
4. Tsuchihashi K, Ueshima K, Uchida T, Ohmura N, Kimura K, Owa M et al. Transient left ventricular apical ballooning without coronary artery stenosis: a novel heart syndrome mimicking acute myocardial infarction. J Am Coll Cardiol. 2001; 38: 11-18.
5. Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M et al. Clinical features and outcomes of takotsubo (stress) cardiomyopathy. N Engl J Med. 2015; 373: 929-938.
6. Akashi YJ, Nakazawa K, Sakakibara M, Miyake F, Sasaka K. Reversible left ventricular dysfunction "takotsubo" cardiomyopathy related to catecholamine cardiotoxicity. J Electrocardiol. 2002; 35: 351-356.
7. Naidech AM, Kreiter KT, Janjua N, Ostapkovich ND, Parra A, Commichau C et al. Cardiac troponin elevation, cardiovascular morbidity, and outcome after subarachnoid hemorrhage. Circulation. 2005; 112: 2851-2856.
8. Scheitz JF, Mochmann HC, Witzenbichler B, Fiebach JB, Audebert HJ, Nolte CH. Takotsubo cardiomyopathy following ischemic stroke: a cause of troponin elevation. J Neurol. 2012; 259: 188-190.
9. Martins R, Barbarot N, Coquerel N, Baruteau AE, Kolev I, Vérin M. Takotsubo cardiomyopathy associated with Guillain-Barré syndrome: a differential diagnosis from dysautonomia not to be missed. J Neurol Sci. 2010; 291: 100-102.
10. Boscá M, Valero C, Pareja A, Bonet M, Boscá I, Sanchez-Roy R et al. Takotsubo cardiomyopathy and status epilepticus: a case report. Eur J Neurol. 2008; 15: 34-35.
11. Valbusa A, Ingrassia V, Rosa GM, Infante MT, Schenone F, Montecucco F et al. Takotsubo cardiomyopathy and torsade de pointes in myasthenic crisis: be aware of QT prolongation. Am J Emerg Med. 2013; 31: 1717-1718.
12. Anand S, Viswanathan S, Arulneyam J. Pulmonary edema in myasthenic crisis. Case Rep Crit Care. 2013; 2013: 863620.

13. Mayor-Gómez S, Lacruz F, Ezpeleta D. Myasthenic crisis and takotsubo syndrome: a non-chance relationship. Rev Neurol. 2012; 55: 725-728.
14. Bansal V, Kansal MM, Rowin J. Broken heart syndrome inmyasthenia gravis. Muscle Nerve. 2011; 44: 990-993.
15. Gautier P, Ravan R, Najjar M, Belhakem A, Ferrier N, Marcaggi X et al. Takotsubo syndrome during normal human immunoglobulin perfusion. Ann Cardiol Angeiol (Paris). 2011; 60: 290-295.
16. Wong CP, Chia PL. Recurrent takotsubo cardiomyopathy precipitated by myasthenic crisis. Int J Cardiol. 2012; 155: e11-e12.
17. Beydoun SR, Wang J, Levine RL, Farvid A. Emotional stress as a trigger of myasthenic crisis and concomitant takotsubo cardiomyopathy: a case report. J Med Case Rep. 2010; 4: 393.
18. Hirose K, Yamaguchi H, Oshima Y, Choraku M, Hirono A, Takamori N et al. Severe respiratory failure and torsades de pointes induced by disopyramide in a patient with myasthenia gravis. Intern Med. 2008; 47: 1703-1708.
19. Sousa JM, Knobel M, Buchelle G, Sousa JA, Fisher CH, Born D et al. Transient ventricular dysfunction (takotsubo cardiomyopathy). Arq Bras Cardiol. 2005; 84: 340-342.
20. Arai M, Ukigai H, Miyata H. A case of transient left ventricular ballooning ("takotsubo"-shaped cardiomyopathy) developed during plasmapheresis for treatment of myasthenic crisis. Rinsho Shinkeigaku. 2004; 44: 207-210.

Correspondence to:

Dr. Héctor Hugo Escutia Cuevas
División de Cardiología. Centro Médico Nacional 20 de Noviembre. ISSSTE.
Avenida Coyoacán Núm. 1617,
Int. APH7, Col. Del Valle Sur,
Deleg. Benito Juárez, Ciudad de México
Celular: 55 39386401
E-mail: perseoyarista@hotmail.com