Myo-Adenylate Deaminase Deficiency (MADD) is a relatively common metabolic disorder of the skeletal muscle. Patients with MADD usually show an impaired bioenergetic production and a clinical spectrum with either exercise-induced muscle pain, fatigue and/or rhabdomyolysis. Left ventricular hypertrophy as well as other types of cardiac involvement have been reported in patients with primary MADD. We describe herein a case of a 61-year-old woman with biochemical and genetic evidence of Myo-Adenylate Deaminase deficiency, in whom we found a right ventricular hypertrophic cardiomyopathy leading to severe outflow tract dynamic obstruction.

Key words: Echocardiography, Myo-Adenylate Deaminase deficiency, neuromuscular disorders, right ventricular disease, right ventricular hypertrabeculation, right ventricular hypertrophic cardiomyopathy

Introduction

Myo-Adenylate Deaminase deficiency (MADD) is a relatively common metabolic disorder of the skeletal muscle firstly described in 1978 (1). The enzyme is one of the most active in the purine nucleotide cycle, playing the adenosine-5-monophosphate deamination and maintaining the high adenosine-5-triphosphate/diphosphate/monophosphate ratio necessary for the bioenergetic metabolism of the working muscle.

Because of the variety of genetic expression of such mutant alleles, the syndrome ranges from asymptomatic carriers to patients showing exercise-induced muscle pain, fatigue, intolerance to exercise, and/or rhabdomyolysis (rare) (2-6).

A morphofunctional involvement of the left ventricle (LV, left ventricular), chiefly consisting of myocardial hypertrophy or hypertrabeculation (HT), has been described in some MADD patients (7, 8).

We report a peculiar case of right ventricular (RV, right ventricle) hypertrophic cardiomyopathy leading to severe dynamic obstruction across the outflow tract.

Case report

A 61-year-old woman presented with a long-lasting history of diffuse myalgias, cramps at lower limbs, fatigue and exercise intolerance. Her family history was unremarkable for neuromuscular disorders, heart diseases and conventional cardiovascular risk factors.

Neurological examination showed mild proximal muscle weakness, more pronounced at lower limbs. Laboratory measurements showed mild CK elevation (397 U/l; reference range, < 200 U/l). Electromyography was unremarkable, whereas muscle biopsy revealed unspecific morphological alterations, but totally absent histochemical staining for MAD. Biochemical study on muscle homogenate also evidenced a virtual absence of MAD activity. Analysis of adenosin-monophosphate-deaminase 1 (AMPD-1) gene identified the common mutation C34T in an homozygous state, which confirmed the diagnosis of MADD.

As routinely scheduled in our neuromuscular patients, she was referred to the cardiology department for heart evaluation.

Physical examination revealed resting heart rate of 75 bpm and sitting blood pressure of 135/80 mm Hg. Intense systolic murmur (Levine grade 4) was electively heard on the pulmonary valve.
Resting ECG (Fig. 1) revealed sinus rhythm (75 bpm), normal atrio-ventricular conduction time (180 ms), right bundle branch block (QRS duration < 120 ms), high S-wave voltage in leads V4-5 and negative T-waves in leads V1-5, with no serious arrhythmias at 24-hour ECG monitoring.

Transthoracic echocardiography showed normal LV morphofunctional indices at rest, but concentric RV hypertrophy (free-wall diastolic thickness 8 mm). Global systolic function was preserved (ejection fraction ≥ 0.60) in both ventricles, with normal fractional shortening. Tricuspid and mitral annulus plane systolic excursion were 20 and 17 mm, respectively. Possible endomyocardial HT was seen in the RV outflow tract (Fig. 2, A-B) to be associated to a muscular obstruction leading to severe dynamic gradient throughout the outflow tract (peak value 60-70 mm Hg) (Fig. 2, C-D).

The patient underwent gadolinium-enhanced cardiac magnetic resonance imaging (MRI), which confirmed the RV free wall hypertrophy, but also demonstrated a giant moderator band, both leading to outflow tract occlusion (Fig. 2, E-F). No signs of RV dysplasia or delay enhancement were recognized.

Discussion

This report shows a novel RV disease in a MADD patient, chiefly consisting with severe hypertrophy of the free wall and the moderator band. These morphofunctional findings may be similar to those from patients with RV arrhythmogenic dysplasia, but the lack of specific MRI findings, delay enhancement, typical premature ventricular beats, epsilon potentials at ECG and myocardial vacuolations allowed us to exclude that cardiomyopathy (9, 10).

Interestingly, prominent trabeculations into the RV, like in our patient, are quite hard to be interpreted properly. In fact, due to its irregular structure, the diagnosis of RV-HT is challenging. The criteria proposed by Jenni et al. (11) and Stollberger et al. (12) for LV-HT barely apply to the RV. As recently emphasized by Limongelli et al. (13) multiple or exaggerated trabeculations can be a normal variant of the RV, and there is no chance for both echocardiography and cardiac MRI to discriminate between the two conditions. Nevertheless, RV-HT has been described in neonatal decompensated hearts (14, 15).

The severe RV dynamic obstruction is of clinical concern because of: a) its influence on patient’s symptoms (fatigue, breathlessness), b) few chances of reducing the gradient noninvasively.

In conclusion, although genetic relationships between neurological and cardiological features are not well defined, this report confirms the need for a comprehensive investigation of the heart in MADD patients, bearing in mind that the above described symptoms could be the consequence of undervalued heart failure.

Acknowledgements

The Authors are grateful to Dr. Gianluca Di Bella for his comments on cardiac magnetic resonance findings.
Figure 2. Ultrasound imaging of the right ventricular hypertrophy and hypertrabeculation (panels A and B) causing severe dynamic obstruction through the outflow tract (panels C and D). Panels E and F show cardiac magnetic resonance imaging in diastole and systole, respectively. Note the hypertrophy of the basal RV free wall and of the moderator band (arrows), both leading to a virtual systolic chamber with outflow tract obliteration. LA, left atrium; LV, left ventricle; RA, right atrium, RV, right ventricle.

References

1. Fishbein WN, Armbrustmacher VM, Griffin JL. Myoadenylate deaminase deficiency: A new disease of muscle. Science 1978;200:545-8.
2. Kar NC, Pearson CM. Muscle adenylate deaminase deficiency: report of six new cases. Arch Neurol 1981;38:279-81.
3. Fishbein WN. Primary, secondary, and coincidental types of myoadenylate deaminase deficiency. Ann Neurol 1999;45:547-8.
4. Fishbein WN. Myoadenylate deaminase deficiency: inherited and acquired forms. Biochem Med 1985;33:158-69.
5. Toscano A, Aguennouz M, Monici MC, et al. Myoadenilate deaminase deficiency: clinical, histochemical and biochemical studies in primary and “coincidental” cases. Ital J Biochem 1997; 46S:170-4.
6. Mercelis R, Martin JJ, de Barys T, et al. Myoadenylate deaminase deficiency: absence of correlation with exercise intolerance in 452 muscle biopsies. J Neurol 1987; 234:385-9.
7. Finsterer J, Schoser B, Stollberger C. Myoadenylate deaminase gene mutation associated with left ventricular hypertrobrubeculation. Acta Cardiol 2004;59:453-6.
8. Skyllouriotis ML, Marx M, Bitter RE, et al. Myoadenylate deaminase deficiency, hypertrophic cardiomyopathy and gigantism syndrome. Pediatr Neurol 1997;17:61-6.
9. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. Circulation 2010;121:1533-41.
10. Bauce B, Basso C, Ramazzo A, et al. Clinical profile of four families with arrhythmogenic right ventricular cardiomyopathy caused by dominant desmoplakin mutations. Eur Heart J 2005;26:1666-75.
11. Jenni R, Oechslin E, Schneider J, et al. Echocardiographic and patho-anatomical characteristics of pathological noncompaction, as a distinct cardiomyopathy. Heart 2001;86:666-71.
12. Stollberger C, Finsterer J. Left ventricular hypertrobrubeculation noncompaction. J Am Soc Echocardiogr 2004;17:91-100.
13. Limongelli G, Pacileo G, Calabrò P, et al. Right ventricular hypertrobrubeculation associated with double-outlet left ventricle: exaggeration of a normal pattern or right ventricular cardiomyopathy? J Cardiovasc Med 2010;11:193-5.
14. Alehan D, Dogan OF. Right ventricular noncompaction in a neonate with complex congenital heart disease. Cardiol Young 2005;15:434-6.
15. Hruda J, Sobotka-Plojhar MA, Fetter WP. Transient postnatal heart failure caused by noncompaction of the right ventricular myocardium. Pediatr Cardiol 2005;26:452-4.