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A CLINICAL CASE OF NON-COMPACTION CARDIOMYOPATHY WITH CONCOMITANT MYOPATHIC SYNDROME AND MUTATIONS IN THE *LMNA* AND *KCNH2* GENES

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A clinical case of a patient with non-compaction cardiomyopathy, early development of life-threatening arrhythmias and conduction disorders, myopathic syndrome and mutations in the *LMNA* and *KCNH2* genes is presented. The issues of diagnostics based on imaging technologies, complex differential diagnostics of non-compaction cardiomyopathy and dilated cardiomyopathy, as well as the basic principles of treatment are discussed. We also present the main provisions of European and American experts on the concept of isolation of lamina-associated cardiomyopathies for mandatory molecular genetic testing and, if identified, early implantation of ICD for the prevention of SCD.

The *LMNA* gene is located on chromosome 1q21. 22, includes 12 exons and encodes two proteins of nuclear intermediate filaments. Lamins A and C are the two main isoforms of nuclear envelope proteins. They are involved in DNA replication, cell cycle regulation, support of nuclear stability differentiation, pore localization, gene expression, and signal transmission. Lamins A and C are widely expressed in skeletal and cardiac muscles [1].

Mutations in the *LMNA* gene cause a number of rare and diverse diseases called laminopathies [2]. The numerous functions, in which a lamin is involved, explain a wide range of diseases for which it may be responsible [1]. Worman H. and Bonne G. [3] suggest 4 main classes of laminopathies according to the main signs and symptoms: diseases of the striated skeletal muscles and the cardiac muscle, lipodystrophy syndromes, peripheral neuropathy and premature aging. Currently, there are at least 12 clinically distinct diseases that exhibit a specific *LMNA* phenotype. Dilated cardiomyopathy (DCM) is the most common form of cardiomyopathy associated with *LMNA* and variants of this gene account for 5 to 10% of the familial form of DCM and 2 to 5% sporadic DCM [4]. However, there is evidence of mutations in this gene in patients with non-compact cardiopathy (NCCM).

Cardiomyopathies associated with *LMNA* are often combined with both tachycardia and bradycardia. Laminopathies are usually associated with supraventricular arrhythmias and conduction disorders, less often with ventricular tachyarrhythmias with a high risk of sudden cardiac death (SCD).

Heart damage in laminopathies, debuting in adults, is often accompanied by musculoskeletal disorders of varying severity: Emery-Dreyfuss muscular dystrophy, lumbar-limbmuscular dystrophy [5], Charcot-Marie-Tooth disease and other peripheral myopathies.

As an example, we present a clinical case of lamin-associated non-compaction cardiomyopathy with concomitant myopathic syndrome.

Patient Z. born in 1970 is a woman with a 'healthy' BMI, her height being163 cm and weight 60 kg. The patient has a family history of arrhythmia (the mother and younger sister both have atrial fibrillation). The first complaints of palpitations, dizziness and weakness appeared at the age of 36. The ECG revealed a sinus rhythm, single supraventricular premature beats, episodes of atrial fibrillation (AF) with a heart rate of 85 bpm. No structural and functional pathological signs were found in echocardiography (EchoCG): LV EDD 48 mm, LV ESD 29 mm, LV EDV 123 ml, LV ESV 47 ml, LV EF 60%.

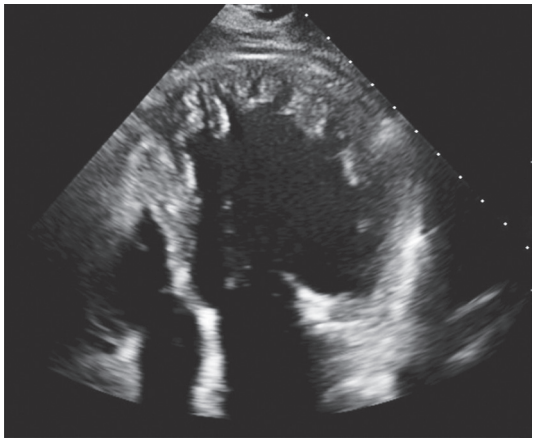

Figure1. Transthoracic echocardiogram. Apical four-chamber projection. Systolic dysfunction of the left ventricle (LVEF 39%). Marked trabecular structure of the LV apex spreading to the anterior-lateral wall in the middle segments, NC/C ratio > 2.1

6 years later, at the age of 42, the patient was hospitalized in the Republican Scientific Practical Center "Cardiology" with clinical signs of heart failure corresponding to NYHA FC III with the complaints of shortness of breath, paroxysmal nocturnal dyspnea, palpitations, presyncope conditions. Percussion of the cardiac region determined enlargement of the heart borders; a diffuse apex beat. Auscultation of the heart revealed muffled heart tones and systolic murmur at the apex of the heart and above the xiphoid process. Signs of moderate hypotrophy of the muscles of the limbs and the muscles of the shoulder girdle with moderately reduced periosteal reflexes were present.

At the age of 45, the patient developed muscle weakness, neurologists verified the diagnosis: Erb's type limb-girdle muscular dystrophy with moderate proximal paraparesis and mild distal in leg extensors. It is difficult to determine the age of the disease onset, but the patient has experienced weakness, difficulties with fast walking, running since childhood. At the age of 45, as the disease progressed, these symptoms intensified, there were changes in posture, and the gait became waddling.

AF with a heart rate (HR) of 75-89 bpm, left anterior fascicular block (LAFB), QTc interval of 430 ms were recorded on the ECG. EchoCG revealed a decrease in the left ventricular ejection fraction (LVEF) to 39%, moderate LV dilation (LV EDD 59 mm, LV ESD 47 mm, LV EDV 140 ml, LV ESV 85 ml), moderate (grade 2) mitral regurgitation, antero-posterior right ventricular size (RV) 21 mm, FAC 40% TAPSE 12 mm, moderate (grade 2) tricuspid regurgitation, pulmonary artery systolic pressure (PASP) 24 mmHg, diffuse hypokinesis and akinesis of the anterior-septum, lower and middle-septum segments of the LV, trabecular structure of the LV apex with spread to the antero-lateral wall in middle segments, NC/C ratio > 2.1(Fig. 1).

According to cardiac magnetic resonance (CMR) imaging data, signs of LV dilatation were revealed (LV EDV 311 ml, LV ESV 191 ml), systolic dysfunction of the LV (LV EF 35%) and RV (RV EF 41%), diffuse hypokinesis. Increased trabeculation of the apex and anterior-lateral wall in middle segments of the LV with a ratio of NC/C > 2.3 were determined according to the Petersen criteria of NCCM (Fig. 2).

The following rhythm disturbances were recorded during 24-hour Holter monitoring: AF with a HR of 69 bpm, VPB > 500 per day, 22 paroxysms of nonsustained ventricular tachycardia (VT) with a HR of 159 bpm, 371 supraventricular premature beats and frequent paroxysms of supraventricular tachycardia with a HR of 135 bpm, episodes of sinus bradycardia with a HR of 36 bpm in daytime and chaotic atrial rhythm, episodes of second-degree SA exit block type I-II (pauses 1.5 - 1.8 s) in the daytime.

A laboratory biochemical study revealed an increase in the level of serum creatine phosphokinase (CPK) – 243 U/L and brain natriuretic peptide (BNP) – 213 pg/ml.

No visible pathological changes of the coronary arteries were detected during coronary angiography.

A genetic study, which was conducted with the consent of the patient, allowed to clarify the diagnosis. NGS sequencing of 174 genes associated with hereditary myocardial diseases was performed. The patient had 2 nucleotide variants in the heterozygote: c.1058A > G (p.Gln353Arg) in exon 6 of the *LMNA* gene and c.3107G > A (p.Gly1036Asp, rs199473022) in exon 13 of the *KCNH2* gene.

Mutation c.1058A > G (p.Gln353Arg) in the *LMNA* gene is pathogenic because it is absent in extensive population studies, but was found in one of 24 examined unrelated families with genetically confirmed laminopathy in Japan [1]. Predictors of pathogenicity in silico also indicate its diagnostic significance.

Additionally, the patient was found to have a variant with uncertain significance (VUS) c.3107G > A (p.Gly1036Asp, rs199473022) in the *KCNH2* gene associated primarily with long QT syndrome (LQT2). This variant has been reported previously in several patients with LQT2 in different studies [6, 7].

Functional analysis in vitro demonstrated a slight decrease in the potassium channel current in the presence of the p.Gly1036Asp mutation [8].

However, this variant has been recorded in some population studies with a low frequency of 0.0001, which, apparently, is an indirect evidence of its low penetrance and milder phenotypic manifestation. In addition, at least one of the described patients with LQTS had an additional and probably pathogenic mutation p.Lys218Glu in the *KCNQ1* gene, also associated with prolongation of the QT interval [9].

Based on the above, the replacement of p.Gly1036Asp in the *KCNH2* gene can have both an independent phenotypic manifestation and can modify and exacerbate the clinical manifestations of mutations in the *LMNA* gene, leading to an elongation of the QT interval and the occurrence of life-threatening ventricular ar-

rhythmias, especially when using certain medications, the appointment of which should be avoided.

For the primary prevention of SCD, the patient underwent implantation of a single-chamber cardioverter defibrillator (VVIR mode) and was prescribed medication: ACE inhibitors (ramipril 5 mg/day), beta-blockers (metoprolol succinate 50 mg/day), aldosterone antagonists (spironolactone 25 mg/day), diuretics (torasemide 10 mg/day) and anticolagulants (rivaroxaban 20 mg).

Against the background of regular medication intake during dynamic 5-year follow-up, the improvement of the patient's clinical status was noted: a reduction of shortness of breath and palpitations, absence of syncopal conditions. In the control EchoCG study, an increase in LV EF up to 50% and a decrease in the progression of negative remodeling of the heart chambers were observed.

Discussion

According to the results of the examination of the EchoCG and CMR, the diagnosis of NCCM in the patient was not in doubt. However, the observed dilated remodeling of the heart with LV systolic dysfunction and the detected mutation c.1058A > G (p.Gln353Arg) in the *LMNA* gene, defects in which are one of the genetic causes (6-8%) of the development of DCM, prompted differential diagnosis with this type of cardiomyopathy. The criteria of NCCM in the presented patient were confirmed using two imaging research methods: 1) according to the EchoCG criteria of Jenni et al. [10], including the presence of a ratio of non-compacted (NC) and compacted (C) layers NC/C > 2.0 at the end of the systole; numerous excessively prominent trabeculae and deep intertrabecular recesses; 2) according to the CMR imaging criteria (Petersen) [11], including an end-diastolic ratio NC/C ≥ 2.3 in one of the LV segments by the long axes of the CMR imaging and the criteria described by A. Jaquier [12] with a proportion of non-compacted myocardium > 20%.

Laminopathies are most often associated with DCM [4]. However, there is evidence of mutations in this gene in patients with NCCM. According to the study, pathogenic variants in the *LMNA* gene were identified in 5% of 95 genotyped patients with NCCM [13].

The conducted studies demonstrated a high proportion of SCD among carriers of the *LMNA* mutation, 46% died suddenly and 12% due to the progression of CHF [5].

Since 2010, the practical recommendations on the genetic diagnosis of cardiomyopathies have been updated with the inclusion of a special position on the diagnosis and treatment of lamin-associated cardiomyopathies [14].

The main provisions of European and American experts coincide on the concept of isolation of lamina-associated cardiomyopathies for mandatory molecular genetic testing and, if identified, early implantation of ICD for the prevention of SCD.

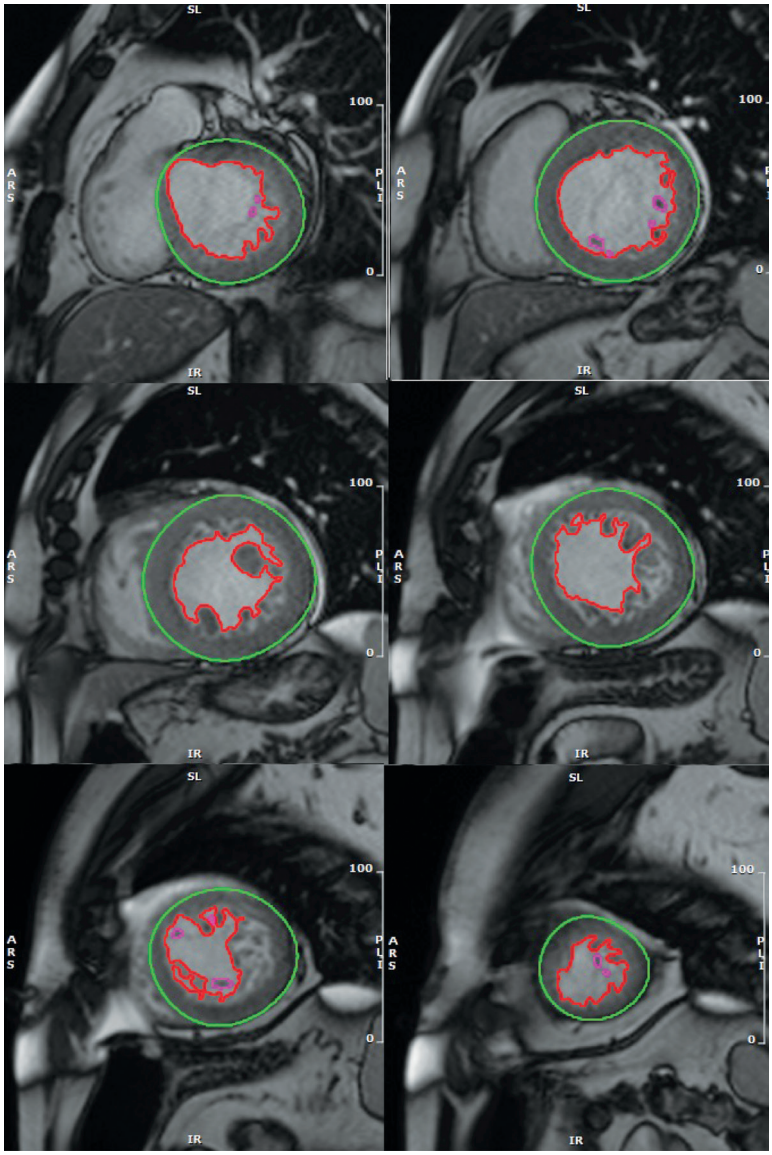

Figure2. MRI of the heart. Dilated phenotype of NCCM with a marked systolic dysfunction (LVEF – 35%). Non-compacted myocardium of the lateral wall of the LV at the level of the middle and apex segments, NC/C > 2.3

Conclusion

Thus, the presented clinical case confirms the idea that laminopathies, along with the myopathic symptom complex, are accompanied by life-threatening cardiac arrhythmias, non-compact myocardial syndrome, as well as an extremely unfavorable prognosis of the disease, which requires preventive implantation of a cardioverter defibrillator. A molecular genetic study is necessary to confirm and clarify the diagnosis of laminopathy.

The authors declare no conflicts of interest.

REFERENCES

1. Astejada M.N., Goto K., Nagano A., Ura S., Noguchi S., Nonaka I., Nishino I., Hayashi Y.K. Emerinopathy and laminopathy clinical, pathological and molecular features of muscular dystrophy with nuclear envelopathy in Japan. *Acta Myol*, 2007, vol. 26, no. 3, pp. 159-164.
2. Worman H.J. Nuclear lamins and laminopathies. *J Pathol*, 2012, vol. 226, no. 2, pp. 316-325. DOI: 10.1002/path.2999.
3. Worman H.J., Bonne G. "Laminopathies": a wide spectrum of human diseases. *Exp Cell Res*, 2007, vol. 313, no. 10, pp. 2121-2133. DOI: 10.1016/j.yexcr.2007.03.028.
4. Parks S.B., Kushner J.D., Nauman D., Burgess D., Ludwigsen S., Peterson A., Li D., Jakobs P., Litt M., Porter C.B., Rahko P.S., Hershberger R.E. Lamin A/C mutation analysis in a cohort of 324 unrelated patients with idiopathic or familial dilated cardiomyopathy. *Am Heart J*, 2008, vol. 156, no. 1, pp. 161-169. DOI: 10.1016/j.ahj.2008.01.026.
5. van Rijsingen I.A., Arbustini E., Elliott P.M., Mogensen J., Hermans-van Ast J.F., van der Kooi A.J., van Tintelen J.P., van den Berg M.P., Pilotto A., Pasotti M., Jenkins S., Rowland C., Aslam U., Wilde A.A., Perrot A., Pankuweit S., Zwinderman A.H., Charron P., Pinto Y.M. Risk factors for malignant ventricular arrhythmias in lamin a/c mutation carriers a European cohort study. *J Am Coll Cardiol*, 2012, vol. 59, no. 5, pp. 493-500. DOI: 10.1016/j.jacc.2011.08.078.
6. Tester D.J., Will M.L., Haglund C.M., Ackerman M.J. Compendium of cardiac channel mutations in 541 consecutive unrelated patients referred for long QT syndrome genetic testing. *Heart Rhythm*, 2005, vol. 2, no. 5, pp. 507-517. DOI: 10.1016/j.hrthm.2005.01.020.
7. Schmitt J., Baumann S., Klingenheben T., Richter S., Duray G., Hohnloser S.H., Ehrlich J.R. Assessment of microvolt T-wave alternans in high-risk patients with the congenital long-QT syndrome. *Ann Noninvasive Electrocardiol*, 2009, vol. 14, no. 4, pp. 340-345. DOI: 10.1111/j.1542-474X.2009.00323.x.
8. Biliczki P., Girmatsion Z., Harenkamp S., Anneken L., Brandes R.P., Varro A., Marschall C., Herrera D., Hohnloser S.H., Nattel S., Ehrlich J.R. Cellular properties of C-terminal KCNH2 long QT syndrome mutations: description and divergence from clinical phenotypes. *Heart Rhythm,* 2008, vol. 5, no. 8, pp. 1159-1167. DOI: 10.1016/j.hrthm.2008.04.016.
9. Steffensen A., Refaat M., David J.P., Mujezinovic A., Calloe K., Wojciak J., Nussbaum R.L., Scheinman M.M., Schmitt N. High incidence of functional ion-channel abnormalities in a consecutive Long QT cohort with novel missense genetic variants of unknown significance. *Sci Rep,* 2015, no. 5, pp. 10009. DOI: 10.1038/srep10009.
10. Jenni R., Oechslin E., Schneider J., Attenhofer Jost C., Kaufmann P.A. Echocardiographic and pathoanatomical characteristics of isolated left ventricular non-compaction: a step towards classification as a distinct cardiomyopathy. *Heart (British Cardiac Society),* 2001, vol. 86, no. 6, pp. 666-671.
11. Petersen S.E., Selvanayagam J.B., Wiesmann F., Robson M.D., Francis J.M., Anderson R.H., Watkins H., Neubauer S. Left ventricular non-compaction: insights from cardiovascular magnetic resonance imaging. *J Am Coll Cardiol*, 2005, vol. 46, no. 1, pp. 101-115. DOI: 10.1016/j. jacc.2005.03.045.
12. Jacquier A., Thuny F., Jop B., Giorgi R., Cohen F., Gaubert J.Y., Vidal V., Bartoli J.M., Habib G., Moulin G. Measurement of trabeculated left ventricular mass using cardiac magnetic resonance imaging in the diagnosis of left ventricular non-compaction. *Eur Heart J,* 2010, vol. 31, no. 9, pp. 1098-1104. DOI: 10.1093/eurheartj/ehp595.
13. Sedaghat-Hamedani F., Haas J., Zhu F., Geier C., Kayvanpour E., Liss M., Lai A., Frese K., Pribe-Wolferts R., Amr A., Li D.T., Samani O.S., et al. Clinical genetics and outcome of left ventricular non-compaction cardiomyopathy. *Eur Heart J*, 2017, vol. 38, no. 46, pp. 3449-3460. DOI: 10.1093/eurheartj/ehx545.
14. Charron P., Arad M., Arbustini E., Basso C., Bilinska Z., Elliott P., Helio T., Keren A., McKenna W.J., Monserrat L., Pankuweit S., Perrot A., Rapezzi C., Ristic A., Seggewiss H., van Langen I., Tavazzi L. Genetic counselling and testing in cardiomyopathies: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*, 2010, vol. 31, no. 22, pp. 2715-2726. DOI: 10.1093/eurheartj/ehq271.

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