Cardiomyopathy with Restrictive-Hypertrophic Phenotype and Initial Morphological Diagnosis "Amyloidosis" as a Manifestation of Danon Disease in a Woman

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Aim. To analyze the difficulties of diagnosis and the clinical features of the Danon disease in women.

Results. An observation of Danon disease in a woman aged 18 years with an uncomplicated family history is presented. The early development of atrial fibrillation (at the age of not more than 15 years) in combination with atrioventricular blockade against the background of regular sports was not attracted due attention for 3 years. The examination revealed: a moderate degree of left ventricular hypertrophy (up to 17 mm), its diffuse nature and simultaneous involvement of the right ventricle, signs of heart failure due to severe restrictive disorders with preserved ejection fraction. Cardiac magnetic resonance imaging data (non-specific late gadolinium enhancement) became the basis for the assumption of amyloidosis and the implementation of a myocardial biopsy. An erroneous diagnosis of cardiac amyloidosis according to myocardial biopsy was refuted during a second study, the PAS reaction revealed signs of storage disease. The diagnosis of Danon disease was verified using DNA diagnostics (c.731delG mutation was detected). Due to the presence of unsustained paroxysmal ventricular tachycardia and a high calculated risk of sudden death, cardioverter-defibrillator was implanted.

The analysis of literature data on the frequency and the manifestation of Danon disease in women, the place of this disease in the structure of the causes of myocardial hypertrophy is given.

Conclusion. Atrial fibrillation at a young age and left ventricular hypertrophy syndrome can develop due to primary myocardial diseases not well known in the practice of a cardiologist. They require an in-depth diagnostic search; their identification is critical for determining treatment tactics and prognosis.

Keywords: hypertrophic cardiomyopathy, Danon disease, amyloidosis, endomyocardial biopsy, atrial fibrillation.

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Introduction

Pathological remodeling and progressive impairment of the heart function at a young age without any obvious external causes suggests the hereditary disorders in most of cases. After excluding of congenital heart defects, the most probable differential diagnosis is represented by myocarditis and cardiomyopathies. The most common variant is hypertrophic cardiomyopathy (HCM), especially in young population, which mainly manifests itself as cardiac hypertrophy, predominantly of left ventricle (LV) myocardium. At the same time, the syndrome of primary (not caused by LV overload) myocardial hypertrophy is very heterogeneous in its genetic nature and requires further diagnostics.

The "classical" HCM (which is the only correct interpretation) is caused, as is already well known, by pathogenic mutations in the genes of various sarcomeric proteins (myosin, myosin-binding protein C, actin, etc.). On the other hand, a wide range of non-sarcomere genetically determined myocardial diseases may lead to LV myocardial hypertrophy – including, first of all, storage diseases (lysosomal, glycogen) along with infiltrative disorders (the most frequently, amyloidosis). The final verification of any variant of primary LV hypertrophy requires DNA diagnostics, however, this stage is always preceded by clinical, instrumental, and in some cases, morphological diagnostics, aiming to identify the disease.

We present a clinical case study of an unusual variant of primary LV hypertrophy in a very young patient (especially for "non-pediatric" cardiologists) with complicated diagnostics in view of the great rarity of this recently described disorder and the variability of its clinical presentation, mostly in women.

Case report

18-year-old woman that was admitted to our hospital (Faculty Therapy Clinic named after V.N. Vinogradov) with signs of dyspnea with moderate exertion (rise the distance between 2 floors) and irregular palpitation in the supine position.

Family history of heart disease at a young age was negative (Fig. 1). Growth and development were aligned with the age. The girl reported normal physical tolerance, played volleyball and went for ski sports.

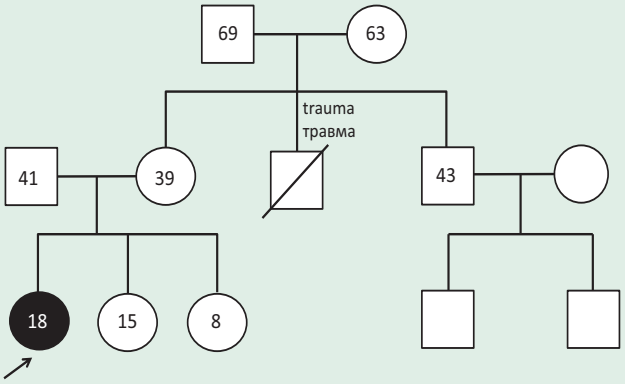
When analyzing medical documentation, we revealed atrial fibrillation (AF) on the ambulatory electrocardiogram (ECG) that had been registered since 2015 (the age of 15 years old), but the patient and her family did not know about it. The girl continued to play sports. She was rather overweight for her age but never referred for screening.

The diagnosis of hypertrophic cardiomyopathy was first determined in 2018 during routine examination for driver license. Since that time, the patient began to experience shortness of breath during physical exertion (climbing to the 3rd floor, playing volleyball). During a physical examination in October 2018, attention was first paid to the presence of AF and ventricular ectopy. The patient was sent to hospital (Altai Regional Cardiology Dispensary).

The echocardiography (ECHO) revealed moderate enlargement of the left atrium (LA) (51 mm), end-diastolic diameter (EDD) of the LV (55 mm), normal ejection fraction (EF) (63%), mild hypertrophy of the interventricular septum (IVS) and posterior LV wall (13 mm) and pulmonary hypertension (pulmonary artery systolic pressure [PASP] of 40 mm Hg). The patient was treated with rivaroxaban 20 mg once daily and was referred to the Altai Regional Cardiology Dispensary in November 2018.

On admission the ECG demonstrated AF with a heart rate (HR) of 86 beats per minute and ventricular extrasystoles. ECHO revealed increased trabecularity of both ventricles (the ratio of non-compact and compact layers was 1.3:1), IVS size was 14 mm. Coronary angiography showed normal coronary arteries. In connection with pauses of up to 4.2 seconds, the started therapy with beta-blockers was discontinued, 2.8 thousand ventricular extrasystoles, 2 paroxysms of unstable ventricular tachycardia were recorded. Taking into consideration pauses of rhythm up to 4.2 seconds, the initial therapy with beta-blockers was discontinued. 24-hour ECG monitoring also revealed 2800 ventricular extrasystoles along with 2 episodes of unsustained ventricular tachycardia.

In order to clarify the etiology of myocardial disease, an endomyocardial biopsy of the right ventricle was per-



All open symbols indicate healthy family members. A proband with cardiomyopathy is indicated by a hatched symbol and marked by an arrow. The age of family members is indicated in the corresponding symbol. According to patient history, more distant relatives didn't present cardiac disease at a young age

Figure 1. Genealogy: family tree of patient G.

formed. The changes were described as subendocardial fibrosis, cardiomyocyte variations (some are thinned, some are hypertrophied) and single peri-myocyte deposits of Congo-positive material. Immunohistochemistry didn't reveal any myocardial inflammatory changes (CD20-positive cells were totally negative, single CD3-positive lymphocytes were detected in interstitial tissue). Considering morphological data in support of amyloidosis, cardiac magnetic resonance imaging (MRI) was recommended. The study demonstrated moderate biatrial enlargement, LV wall hypertrophy (IVS size up to 17 mm) and increased trabecularity of both ventricles with non-specific delayed contrast enhanced in the myocardium. The patient continued therapy with rivaroxaban and was referred to our hospital (Faculty Therapy Clinic named after V.N. Vinogradov) due to suspected cardiac amyloidosis.

On physical evaluation the patient was stable and had state of moderate severity. The skin had normal color and humidity with white scars of striate atrophy on the lateral surfaces of the skin of the abdomen. The height was 168 cm; the weight was 80 kg (body mass index 28.3 kg/m^2). There was no swelling. Lung auscultation revealed vesicular breathing without rales, respiratory rate was 16 per minute. Heart sounds were irregular, muffled, with heart rate of 64 beats per minute. No other abnormal sounds during heart auscultation were present. The blood pressure level was 140/80 mm Hg. Palpation of the abdomen didn't reveal any abnormalities.

Routine blood tests demonstrated only a slight increase in the level of aspartate transaminase (52 units/l) and lactate dehydrogenase (718 units /l), otherwise without deviations from the normal value. The level of creatine kinase was 92 units /l. An immunological study revealed an increase in the level of anti-O-streptolysin (349 units /ml; normal rate under 200) and antibodies to antigens of cardiomyocyte nuclei in a minimal dilution (1:40). Therewith the level of antibodies to endothelial antigens, cardiomyocytes and fibers of the cardiac conduction system was normal. Blood viral polymerases chain reaction (PCR) analysis for cardiotropic viruses was negative. Urine tests were normal.

ECG (Fig. 2) during in-hospital period demonstrated AF with heart rate of 58-74 beats per minute and single premature ventricular contractions. There were signs of LV myocardial hypertrophy (Sokolov-Lyon index of 44 mm), negative T waves in I, II, aVL, V5-V6 leads, QRS duration of 118 ms, QT/QTc intervals of 418/464 ms. Holter ECG monitoring was performed under 2.5 mg bisoprolol therapy. Study results demonstrated the maximal duration of rhythm pause of 3632 ms along with 1397 short pauses (2000-3000 ms) during the day. Average heart rate was 65 bpm during daytime (50-101 bpm) and 54 bpm during the night (38-71 bpm). Ventricular extrasystoles were polymorphic with the overall amount of 1954 during the follow up period (35 couplets, 4 triplets, 5 runs of non-sustained ventricular tachycardia [4-8 RR] with a heart rate of 120 bpm, mainly in the daytime). Changes of ST-T segment were not revealed. Chest x-ray demonstrated the signs of pulmonary congestion.

ECHO (Fig. 3) showed enlargement of LA (56 mm, 144 ml, 75 ml/m^2), LV EDD of 55 mm, severe symmetric LV hypertrophy (IVS 15 mm, posterior wall up to 17 mm) with high trabecularity. End-diastolic LV volume was 137 ml (71 ml/m^2), end-systolic LV volume was 53 ml, with LV ejection fraction level of 61%. Local contractility was normal but significant LV diastolic dysfunction was demon-

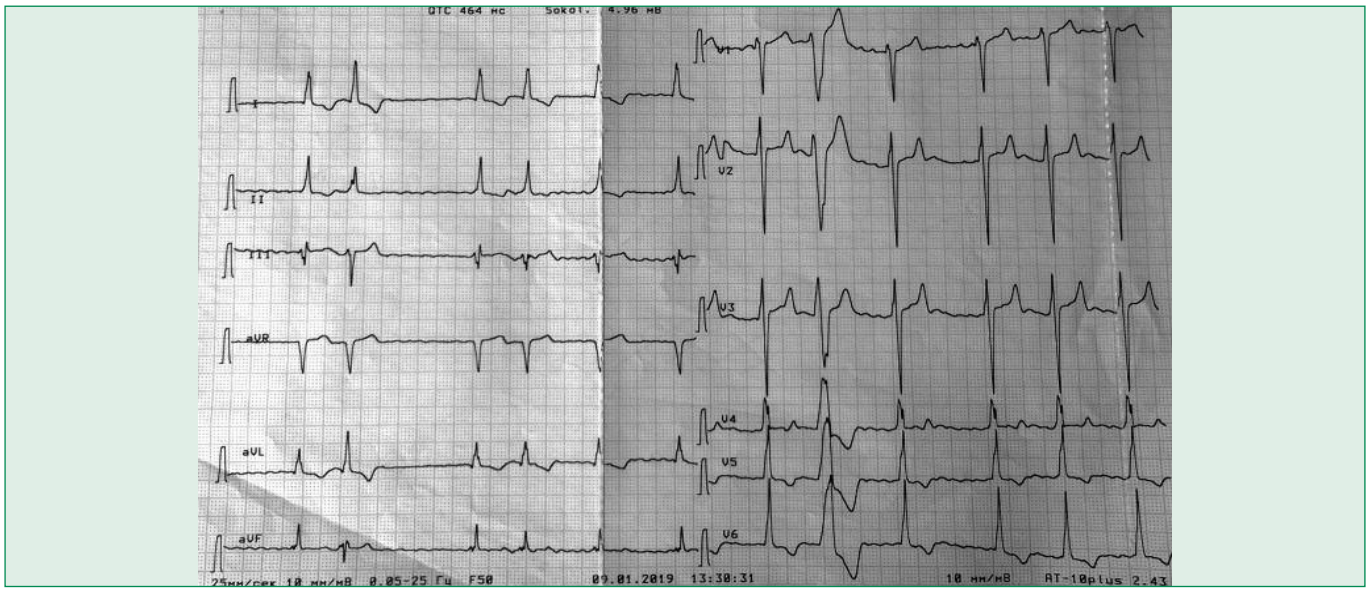
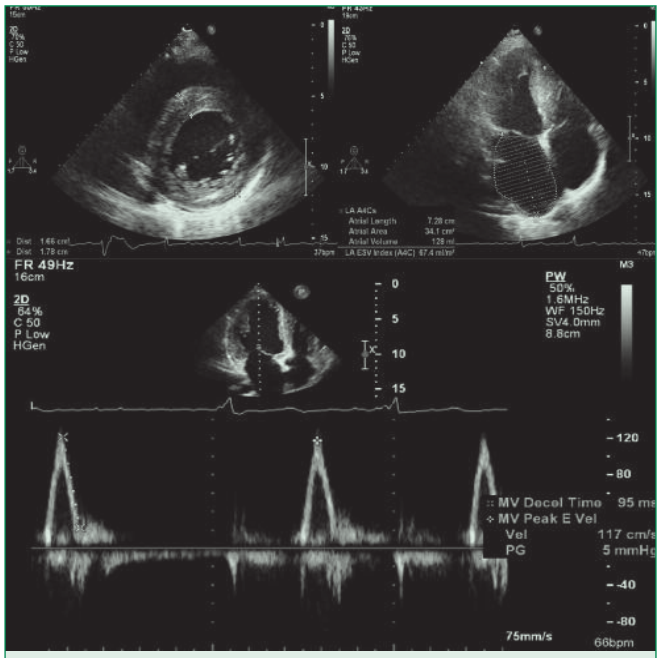


Figure 2. Electrocardiogram of patient G. on admission (description in the text)



On the left – signs of diffuse left ventricular myocardial hypertrophy (1.7-1.8 cm), in the center – significant dilatation of the left atrium as a result of restriction, on the right – restrictive type of diastolic dysfunction (DecT 96 ms)

Figure 3. Echocardiograms of patient G., 18 years old

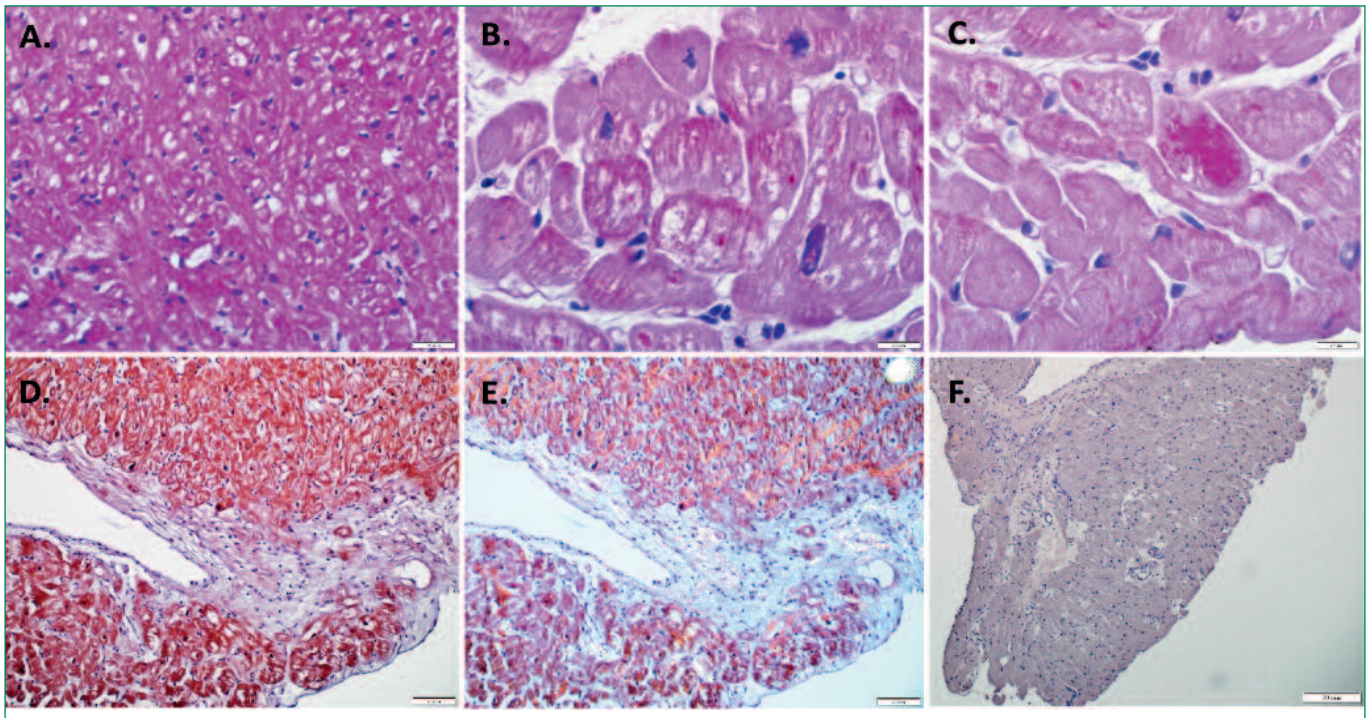
strated (DecT 95 ms, E/med E` 20.3; E/lat E` 10.4). What stands out in the report is the hyperechogenicity of the LV myocardium which could indicate some variants of storage diseases. Right ventricle diameter was 27 mm whereas wall thickness was 8 mm with TAPSE of 19 mm and right atrium volume of 64 ml (33 ml/m^2). There was found minimal regurgitation on the mitral and tricuspid valves (I degree) and moderate pulmonary hypertension (PASP of 45 mm Hg). The inferior vena cava was dilated with less than 50% collapse on inspiration. The signs of mild pericardial effusion (less than 100 ml) and separation of pericardial leaves up to 6 mm were also present.

Thus, the presence of diffuse hypertrophy of the left (up to 17 mm) and right (up to 7 mm) ventricles with preserved systolic function was confirmed. Considering the patient's age, early manifestation of AF and LV hypertrophy, signs of severe LV hypertrophy syndrome on ECG along with preserved systolic function, the diagnosis of amyloidosis seemed extremely unlikely. According to blood and urine tests, free light chains of immunoglobulins were not detected.

Histological samples (endomyocardial biopsy of the right ventricle) were evaluated at the Chair of Pathological Anatomy (named after Acad. A.I. Strukov). The samples consisted of four pieces of the wall of the right ventricle, that were not oriented. The signs of endocardial sclerosis were found. Myocardium was evaluated and represented irregular hypertrophy of cardiomyocytes with large foci of sclerosis. Cardiomyocytes demonstrated an "empty" cytoplasm in the perinuclear zone. Mild sclerosis was confirmed when stained according to van Gieson. No data were obtained for amyloid deposition in polarized light and in staining of Congo red (Fig. 4). In addition, staining with a periodic acid-Schiff (PAS) reagent was performed, which showed a positive reaction (accumulation of a PAS positive substance under the sarcolemma, single cardiomyocytes contained large PAS positive granules, that are completely filled with PAS positive material). There was no evidence of the random arrangement of cardiomyocytes, and this fact along with myocardial hyperechogenicity revealed during ECHO study significantly increased the probability of diagnosis of the storage disorders.

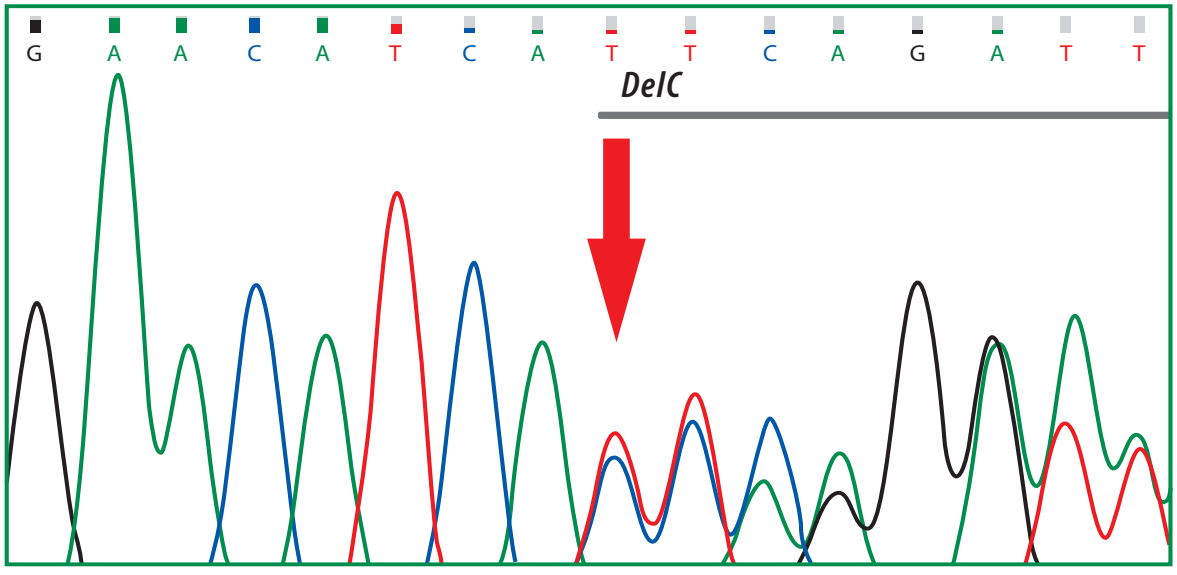
The patient was referred to genetic counseling. According to clinical and laboratory data the storage diseases (cardiac form of glycogenosis? lysosomal storage disease? fatty acid oxidation disorder?) appeared to be the most likely diagnosis. Additional blood tests were performed for targeted DNA diagnostics in the genes *PRKAG2* (cardiac glycogenosis), *LAMP2* (Danon disease) and *XGAL* (Fabry disease). The absence of extracardiac symptoms and negative family history makes lysosomal storage diseases (including Danon disease) less likely, but does not allow them to be excluded. It is not also inconceivable that patient could present symptoms of sarcomeric cardiomyopathy with a restrictive-hypertrophic phenotype considering high trabecularity of LV. In the absence of diagnostic findings in target genes, full-exom sequencing was planned, in view of the wide variety of genetic types of glycogenoses and mitochondrial diseases.

Taking account of transient atrioventricular block, we didn't increase the dose of beta-blockers (bisoprolol was given in the dose of 1.25 mg at the time of discharge) and could not prescribe class III antiarrhythmics as there were indications for permanent cardiac pacing. In addition, the estimated risk of sudden death using the HCM Risk-SCD calculator was 8.9% during 5 years. Due to the risk score value the patient was recommended the implantation of a cardioverter-defibrillator (ICD). The risk of thromboembolic complications (score of 1 according to the CHA_2DS_2-VASc scale) along with the presence of a non-compact myocardium and severe restrictive changes with a significant LA dilatation contributed to prolongation of the anticoagulation therapy. Additionally, perindopril 5 mg, spironolactone 25 mg and torasemide 5-10 mg were prescribed. The condition of the patient improved with reduced dyspnea intensity and increased physical tolerance.



A – staining with hematoxylin-eosin (hypertrophy of cardiomyocytes, perinuclear vacuoles in the cytoplasm); **B, C** – periodic acid-Schiff reaction (accumulation of a PAS-positive substance of violet color under the sarcolemma, diffuse in the cytoplasm in individual cardiomyocytes); **D, E** – staining with Congo red (at the regional hospital in Barnaul) – brick-red staining of the cytoplasm of cardiomyocytes (**D**), which in polarizing light gives a non-specific orange glow (**E**); **F** – second staining with Congo red (at the Sechenov University), negative reaction

Figure 4. Endomyocardial biopsy samples of the right ventricle of patient G., 18 years old



The site of a single nucleotide deletion c.731C (p.Thr244fs) is marked by an arrow

Figure 5. Fragment of direct sequencing by Senger in exon 5 of the *LAMP2* gene

It was recommended to avoid playing sports. A few months later an ICD was implanted for primary prevention. During follow up period there was no ICD shocks or arrhythmic events registered.

At the first stage of DNA diagnostics by Sanger sequencing, a deletion of c.731delC in a heterozygous state was detected in the *LAMP2* gene, which made it possible to verify Danon disease in this clinical case report (Fig. 5).

Discussion

This clinical observation is considered to be unique because very rare disease with the incomplete manifestation of its systemic symptoms in a young woman had been presented. Danon disease – one of the rare few X-linked dominant diseases that was described only in 1981 and represents the hereditary lysosomal storage disorder associated with impaired process of autophagy. It is based on mutations in the *LAMP2* (lysosomal-associated membrane protein 2) gene. The most characteristic feature of Danon disease is its extremely unfavorable prognosis – with progression of chronic heart failure (CHF) and cardiac arrhythmias by the age of 20 while male patients practically do not survive to the age of 30 years in the absence of heart transplantation.

Clinical and instrumental diagnostics is also based on several characteristic signs, such as diffuse severe myocardial hypertrophy (in typical cases, the thickness of the LV myocardium in patients of "non-pediatric" cardiologists exceeds 30 mm) with a progressive impairment in LV EF and severe restrictive diastolic disfunction, which contributes to extremely unfavorable combination and leads to a rapid progression of heart failure. The hypertrophic tissue is acoustically heterogeneous with specific "striated" appearance in the M-mode and deep clefts within the ventricular myocardium that meet the criteria of a non-compact myocardium. On ECG, in addition to LV hypertrophy criteria (Sokolov-Lyon index can exceed 10 cm), signs of pre-excitation are often detected (shortened PQ interval).

Extracardiac manifestations of the disease include intellectual deficit, muscle weakness, and retinopathy (retinitis pigmentosa). Blood tests may reveal increased level of creatine kinase and liver enzymes while morphological examination demonstrates PAS-positive, small cytoplasmic inclusions in cardiac myocytes. An immunohistochemical study, which may exclude the presence of LAMP2 protein, is also highly informative, but this test is beneficial only in men with genetic mutations that disrupt normal protein expression. The diagnosis is confirmed or excluded by DNA diagnostics in the *LAMP2* gene (the disease, as far as is known today, is monogenic). Its prevalence, even among other forms of primary HCM, is less than 5% [1], while in our own registry of 46 patients with primary myocardial hypertrophy it has reached 4% [2]. But it must be emphasized that both of our patients with Danon disease from this register were males who had not only massive (up to 30 mm) LV hypertrophy, but additionally typical extracardiac manifestations of the disease (mental retardation, increased levels of liver enzymes and creatine kinase). Taking in consideration the above, the diagnosis of Danon disease had been most likely even before the DNA diagnostic results were obtained.

In the case mentioned above, even though the storage disorder appeared to be the most probable cause of myocardial hypertrophy, Danon disease was far from the first among the possible diagnoses. In addition, it was impossible to completely exclude the true (sarcomeric) variant of HCM. As it usually happens, HCM represented the first diagnosis in young patient of 18 years old, and there were reasons for this (severe LV hypertrophy, far beyond the "sports heart"). Nevertheless, there were some clinical features that raised doubts as to the diagnosis of "traditional" HCM: extremely early presentation of stable AF combined with impaired AV conduction and progressive CHF in the absence of ventricular outflow tract obstruction. The decompensated form of sarcomeric HCM is not frequent and is represented in less that 5% of overall number of patients with sarcomeric variants of disease (it usually diagnosed during the first 8 years since the manifestation of symptoms) [3]. Additionally, we focused in this case report on the fact that signs of ventricular outflow tract obstruction were lacking while right ventricle myocardium was affected. It is also not typical for HCM and may contribute to further screening of other cardiac disorders.

It seems quite unusual that there was no adequate consideration of the symptoms in young patient, without any medical screening and treatment for at least 3 years after the manifestation of stable AF. The patient was not informed about her disease and continued to be active in sports until the onset of severe dyspnea. History of active participation in competitive sports also initially caused doubts about Danon disease – as it was usually characterized by slowly progressive course of distal myopathy, which could exclude the possibility of high-intensive physical activity such as skiing and volleyball. Only at regional hospital (Altai Regional Cardiology Dispensary) it was possible to perform thorough medical examination including cardiac MRI and endomyocardial biopsy but it wasn't enough for correct nosological diagnosis. Further course of events appeared to be dramatic as the morphological data was misinterpreted in support of amyloidosis. But at our hospital after reconsideration of endomyocardial biopsy stained with Congo red under polarized light we didn't reveal typical signs of cardiac amyloid (light-green hue) that stressed again the importance of such diagnostic test for all patients with suspected amyloid. Endomyocardial biopsy was re-stained with Congo red in our laboratory but the result was also negative. In addition, staining with a PAS reagent was performed, which should always be

used in cases of suspected storage diseases, and this test turned out to be informative. However, even before obtaining the results of morphological study, the diagnosis of amyloidosis almost completely could be ruled out. And this is primarily due to the age of the patient – because at the age of 15-18 years the prevalence of cardiac amyloidosis is extremely low. The heart is affected in several forms of amyloidosis (congenital and acquired transthyretin forms, primary AL, very rarely AA amyloidosis), however, none of these forms is observed in children. The primary AL-amyloidosis is characterized by earliest manifestation (but usually not earlier than the age of 30 years), however, it represents also the most unfavorable form of heart amyloidosis, which, as a rule, leads to the death of patients in first three years if not treated. In our clinical case the patient had no signs of a system lesions that were typical for AL-amyloidosis or myeloma. In addition, we used method for the estimation of the free light chains of immunoglobulins in serum in order to rule out the diagnosis of amyloidosis, and this test provided predictably negative result.

Except young age of the patient, the ECG findings also were contrary to the diagnosis of amyloidosis: as it known, in case of verified cardiac amyloidosis, there may not be low voltage of QRS complexes with pathological Q waves or QS complexes [4], but such severe LV hypertrophy syndrome is not typical for them. Traditionally ECG criteria of LV hypertrophy are usually observed in «true» storage disorders (when the pathological substance accumulates inside cardiomyocytes and leads to their pseudohypertrophy), while in infiltrative diseases (including cardiac amyloidosis), an electrically inactive area is deposited around cardiomyocytes, subsequently contributing to a significant decrease in amplitude of electrical signal.

The protocol of cardiac MRI was not convincing for either amyloidosis or any other storage disease. In addition to amyloidosis, which is characterized by diffuse subendocardial accumulation of gadolinium, a relatively specific pattern is described in Fabry disease (accumulation in the basal parts of the inferolateral LV wall [5]), however, contrast accumulation in the same areas may be observed in patients with Danon disease and some mitochondrial myopathies. That's why this method alone is not enough for precise diagnostics.

In the present case the objective clinical picture of the patient was not fully pathognomonic for any of the storage diseases (there was no kidney damage, neuropathy, retinitis pigmentosa, diabetes mellitus, skeletal dysplasia, myopathy, angiokeratum, etc.), so differential diagnostics between several variants of cardiomyopathy was required, that could only be effective based on detection of pathogenic mutations. Among other options, only an immunohistochemical study on the LAMP2 protein in the myocardium was not used (however, Danon disease was not the most probable diagnosis and this test would be positive in women). Also, the level of lactate and pyruvate was not estimated but it could be relevant in case of mitochondrial cardiomyopathies. At the same time, measurement of alpha-galactosidase concentration is of little value for Fabry disease diagnostics in women. Technology of DNA diagnostics (up to genome-wide sequencing after negative results of targeted studies) appeared to be the most optimal and quickly contributed to correct identification of a disease.

The stages of diagnosis can be represented as follows: identification of LV myocardial hypertrophy – determination of its primary etiology – obtaining data in favor of storage disease (uncertainty of true, sarcomeric HCM diagnosis) – misleading nosological, clinical and laboratory diagnosis (including suspicion of amyloidosis based on the endomyocardial biopsy) – targeted genetic diagnosis. It should be noted that all these diagnostic stages may not include the procedure of biopsy considering the extremely low probability of amyloidosis at the age of 18 years. Additionally, endomyocardial biopsy does not provide enough information for the differential diagnostics between storage diseases, usually confirming only a group diagnosis (based on accumulation of PAS-reagent). In view of this, morphological examination has its advantages but could not be obligate. Compared to above mentioned technologies, timely DNA diagnostics appears to be the most optimal in a given setting.

There have been reported several case series of Danon disease in women according to data of literature [6-8]. Based on analysis of more than 146 published cases, the proportion of females was up to 38% of patients [9]; where main clinical features included not only a lower rate of extracardiac manifestations, but also a more frequent detection of the dilated cardiomyopathy (29.3%); while cardiac hypertrophy was revealed in 96.2% of cases among male patients. In general, as is characteristic of X-linked dominant diseases, women have less severity compared to men, however, there are also cases of cardiac transplantation due to terminal heart failure among females over 40 years old [10]. Nevertheless, sudden death in patients with signs of pre-excitation and AV block on ECG was also reported. This fact was estimated by the authors as a variant of the arrhythmogenic phenotype of the disease [11]. At the same time, before the manifestation of cardiac arrhythmias, these women could remain asymptomatic, presenting only structural changes in the myo-

cardium (for example, delayed contrast accumulation according to MRI data). Therewith, author team from China reported series of clinical observations, where three female patients with pathogenic mutations in the *LAMP2* gene remained asymptomatic despite ECG changes and moderate LV hypertrophy according to ECHO data [8]. More recently, results of the Spanish registry of patients with Danon disease were published. The study included the observation of the 27 patients, where significantly higher prevalence of extracardiac manifestations was registered among males (80% of study participants presented signs of myopathy, 83% – learning disorders and 63% – vision impairment) compared with the rates (5%, 0% and 27%, respectively) among female patients [7]. Cardiac symptoms manifested in women later than in male patients (on average, at the age of 37 and 23 years old, respectively), whereas adverse outcomes (death/heart transplantation) after 4 years of follow-up occurred less frequently (in 43% and 67% of cases, respectively). Nevertheless, such course of disease could not be regarded as favorable either. Based on multivariate analysis, data demonstrate that adverse outcomes occurred in male and female population equally often (in 37% and 32% of cases), but in women such events were registered at later date (on average, at the age of 21 and 38 years old, respectively) [9].

Preventive therapy in patients with Danon disease represents the most controversial question that is also crucial for other genetically determined cardiomyopathies. It comprises algorithms of cardiac sudden death prevention among asymptomatic or low-symptomatic mutation carriers, that would be more typical for women. That was to be expected that considering limited experience in the field of diagnostics and treatment of Danon disease along with the leading role of heart failure in the structure of mortality, specific clinical guidelines for ICD implantation have not been developed yet. In majority of cases, the risk of sudden death is estimated using the HCM Risk-SCD calculator proposed primarily for sarcomeric HCM [1], whereas official current guidelines for ICD implantation in dilated cardiomyopathy are also applicable to many patients with Danon disease at the stage of CHF decompensation (including those awaiting heart transplantation).

In our case the clinical decision was based upon the presence of indications for permanent cardiac pacing (considering atrioventricular block with episodes of ventricular asystole of more than 3 seconds and inability of further beta-blockers up-titration) in combination with unstable ventricular tachycardia that was estimated as potential predictor of sudden cardiac death. Taking into consideration severe LV hypertrophy and LA dilatation, the calculated risk of sudden death exceeded 8% – in this situation, the implantation of dual chamber pacemaker could not be an optimal option. There could be potentially expected the deterioration of heart failure due to progression of fibrotic changes (it was described in explanted hearts [11], but we had not yet observed such structural changes) that may require heart transplantation. In view of the already existing heart failure, the patient was recommended to avoid pregnancy, although cases of successful gestation in asymptomatic women have been described [11]. Definitely it was also not recommended to continue sports activities. It is crucial for patient to prolong careful monitoring with follow up visits not less than twice a year in order to prevent complications and provide optimal treatment tactics.

Conclusion

An unusual clinical observation of Danon disease in young woman of 18 years old without family history but with verified DNA diagnostics (positive mutation in c.731delG gene) was presented. It is also worth noticing that this rare pathological condition was diagnosed in a young woman with extremely early onset of AF (at the age of 15 years) in combination with hemodynamically significant atrioventricular block at a time when she regularly played competitive sports without any adequate medical consideration over the course of 3 years. Additionally, the patient had the misdiagnosis of cardiac amyloidosis according to myocardial biopsy despite the moderate diffuse LV hypertrophy (IVS thickness up to 17 mm) with simultaneous involvement of the right ventricle and progression of heart failure due to severe restrictive disorders in the setting of preserved LV EF. Further genetic testing using DNA diagnostics made it possible to verify Danon disease in this clinical case report. During follow up period the patient remained stable, she continued to take anticoagulant and cardiotropic therapy. Considering unsustained episodes of ventricular tachycardia, indications for permanent cardiac pacing and a high estimated risk of sudden death, ICD was implanted for primary prevention. Systematic medical monitoring is recommended in order to prevent potential complications and timely schedule heart transplantation as may be required.

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