Hypertrophic cardiomyopathy or hereditary hemochromatosis? (RCD code: III-2B.3.o)

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Abstract

Hemochromatosis is a disease resulting from excessive deposition of iron in parenchymal tissues. The most common form of this disease is associated with the homozygous p.Cys282Tyr mutation of the HFE gene. It leads to multisystemic disease including iron overload cardiomyopathy. Heterozygotes usually do not express a hemochromatosis phenotype, however there are known cases of iron overload in this group of patients. We present a case of 48-year old man, with family history of hereditary hemochromatosis, p.Cys282Tyr mutation carrier, who was admitted to cardiology department due to persistent atrial fibrillation episode. Laboratory tests revealed transferrin serum iron saturation value of 47.8% with other parameters of iron metabolism within the reference range. Transthoracic echocardiographic study showed image consistent with hypertrophic cardiomyopathy. Sinus rhythm was successfully restored by synchronized electrical cardioversion. Based on cardiovascular magnetic resonance imaging cardiac iron overload cardiomyopathy was ruled out. He was discharged home in good general condition without symptoms. JRCD 2016; 3 (1): 24–27

Key words: rare disease, iron overload cardiomyopathy, atrial fibrillation, echocardiography

Case presentation

A 48-year old man was admitted to the emergency department and afterwards to cardiology ward due to atrial fibrillation episode (AF). He had past medical history of persistent AF in the course of which he had been taking dabigatran and metoprolol. Four years ago the patient underwent coronary angiography which did not show significant atherosclerotic changes. Furthermore, he had family history of hereditary hemochromatosis (HH) and was known to be p.Cys282Tyr mutation carrier (Figure 1). The patient came to the hospital due to arrhythmia episode lasting for 15 hours and complained about non-characteristic chest pain. On physical exam he had good general appearance, his vital signs were normal, his skin had normal color, he did not present any neurological deficits. Examination was unremarkable besides clinical signs of AF with heart rate of 90 beats per minute. He didn’t complain of HH symptoms like fatigue or arthralgia.

Laboratory tests on admission drawn attention to increased N-terminal brain natriuretic peptide concentration (2364 pg/ml, reference range <300 pg/ml). Blood levels of cardiac troponin I was slightly increased without a dynamic pattern of values characteristic for myocardial infarction and the MB fraction of creatine kinase (CKMB) was within the reference range. Laboratory testing showed normal serum concentration of iron (24.9 µmol/L, reference range 11–28 µmol/L) and ferritin (272.3 ng/mL, reference range 30–400 ng/mL). Total iron binding capacity (TIBC) was also within the reference range (52.1 µmol/L, reference range 40–70 µmol/L), transferrin serum iron saturation (TS) was 47.8% (reference range 20%-50%). Liver function tests (LFT) and blood glucose level were within reference range. A standard 12-lead electrocardiogram (ECG) showed AF with heart rate of 90 beats per minute, left axis deviation, left anterior fascicular block, QRS interval of 100 ms, positive-negative T waves in leads I, aVL, V2-V3, and flattened in leads II, III, aVF and negative in leads V4-V6. Left ventricular hypertrophy criterion in left anterior fascicular block was met: S in III + (maximal R + S in one of the precordial leads) >3.0 mV (Figure 2) [1].

Transthoracic echocardiographic study showed enlarged left and right atrium (respectively 59 mL/m² and 37 cm²), normal size of other heart chambers, global systolic function of the left ventricle with ejection fraction (EF) of 50% without segmental wall motion abnormalities. The study revealed asymmetrical left ventricle (LV)
hypertrophy, which was most strongly expressed in interventricular septum middle segment (22 mm), consistent with hypertrophic cardiomyopathy (HCM). There was no evidence of significant LV outflow tract obstruction at rest, after Valsalva maneuver and after exercise. Color Doppler showed moderate mitral regurgitation. There were no echocardiographic signs of right ventricular dysfunction or pulmonary hypertension, or pericardial effusion (Figure 3).

Heterozygotes for the C282Y mutation of the HFE (full name: hemochromatosis) gene usually do not express a hemochromatosis phenotype, however there are known cases of iron overload in this group of patients. Therefore in the differential diagnosis in this case we considered non-obstructive HCM and iron overload cardiomyopathy due to HH.

**Figure 1.** Hereditary hemochromatosis pedigree of patient’s family. His father had been suffering from HH and despite ongoing treatment died of the disease. His brother is a C282Y mutation carrier and has no clinical manifestations of HH. His sister and his children haven’t been tested genetically. Square – male; circle – female; crossed figure – deceased; empty figure – unaffected; filled figure – affected; half-filled figure – heterozygous for recessive allele.

**Discussion**

**Definition and etiology**

Hemochromatosis is a rare disease resulting from excessive deposition of iron in parenchymal tissues which may be due to inherited genetic disorder or secondary to excessive oral or parenteral intake of iron. The most common form of HH is an autosomal recessive disorder related with C282Y mutation in the HFE gene [2]. Less often HH is associated hemojuvelin, hepcidin, ferroportin, or ceruloplasmin genes mutations [3]. Iron overload leads to multisystemic disease including liver cirrhosis, cardiac disease – heart failure or conduction defects, diabetes mellitus, hypopituitarism and hypogonadism, hypothyroidism, skin hyperpigmentation, arthropathy, especially involving the second and third metacarpophalangeal joints. Hepatocellular carcinoma is one of the most serious complications of the disease, which leads to approximately 45 percent of all deaths in patients with HH [4].

**HFE-associated hereditary hemochromatosis**

The most common form of HH is associated with the homozygous C282Y mutation of the HFE gene (HFE-associated hereditary hemochromatosis, HFE-HH). Epidemiological studies have shown that frequency of that mutation is high, with a prevalence of 1:200 to 1:250 for homozygosity and 1:8 to 1:12 for heterozygosity in Caucasian populations [5]. HFE gene encodes a transmembrane protein responsible for iron uptake regulation in the intestine and liver. Inappropriate low secretion of hepcidin, which negatively regulates iron absorption, is postulated to be involved in HH development [6]. Biochemical features of iron overload are: elevated TS and serum ferritin concentration. What is important in clinical setting TS is an early and reliable marker, however, it does not correlate with the clinical course of the disease. On the other hand, serum ferritin concentration increases progressively over time according to the degree of iron overload [6].

Heterozygotes for the C282Y mutation of the HFE gene usually do not express a hemochromatosis phenotype. So far, studies have shown that in a group of 1058 heterozygotes mean TS values were higher than in normal subjects. TS levels exceeding the threshold associated with the homozygous genotype were found in 4 percent
Holcman, et al.

of male and 8 percent of female heterozygotes [7]. A potential role of acquired factors, such as excess alcohol intake, diabetes and liver diseases have been proposed to explain the occurrence of iron overload in those heterozygotes [8]. On the other hand, there has been identified an associated genetic defect – the compound heterozygous state for C282Y and the widespread p.His63Asp (H63D) variant allele [8]. Compound heterozygotes for C282Y/H63D heterozygosity has been reported to occur in 2–5 percent of cases of HH with a phenotypic expression of iron overload [9-11]. Compound heterozygotes for C282Y and the p.Ser65Cys allele has been reported to display very mild HH [8].

Risk stratification and management

Mortality during the course of HH correlates with the degree and duration of iron overload [6]. In adult patients mutation analysis is indicated when TS is higher than 45 percent. Conformation of HFE-HH is possible in case of presence of C282Y homozygosity or C282Y/H63D compound heterozygosity. Absence of these mutations shows that iron overload is probably arising from other causes [6]. The 2011 guidelines from the American Association for the Study of Liver Diseases recommend cutoff levels for TS higher than 45 percent and serum ferritin value greater than 200 ng/mL in men and greater than 150 ng/mL in women for screening patients with iron overload [3,12]. Therapeutic management includes phlebotomy in selected patients and rarely chelating agents are used in order to remove excess iron from the body.

Iron overload cardiomyopathy

Theoretically there is a possibility of overlap between HH and HCM, however it would be extremely rare. It has been previously shown by A. Hildebrand et al. that in patient with HCM, secondary hemochromatosis may occur due to an excessive parenteral intake of iron [13]. According to the proposed classification by the Centre for Rear Cardiovascular Diseases, HCM with hemochromatosis should be classified as hypertrophic cardiomyopathy with metabolic disorder (CRCD code class III-2B.3.o) [14]. By definition iron overload cardiomyopathy (IC) refers to a secondary form of cardiomyopathy resulting from the accumulation of iron in the myocardium [15]. Importantly, one third of deaths in HH, especially in young male patients is believed to be due to IC [2]. In the course of IC ferrous iron (Fe2+) enters the myocytes through the voltage-dependent L-type calcium channels [16,17]. This process takes place primarily in ventricular miocardium and later in the atria [16]. Reactive oxygen species formation leads to peroxidation of membrane lipids, cellular proteins, and nucleic acids. Furthermore, the process impairs cardiomyocyte calcium transport, which results in development of the diastolic and systolic ventricular dysfunction seen in association with iron overload [16]. Two main phenotypes of IC have been identified: the dilated and the restrictive phenotype, but there might also be developed conduction system abnormalities, tachyarrhythmias, and perimyocarditis. The most commonly observed is the first type of cardiomyopathy leading to left ventricle dilatation and reduced systolic function [16].

Cardiovascular magnetic resonance imaging (CMR) with T2* relaxometry enables quantitative assessment of cardiac iron deposi-
tion. This method accurately predicts tissue iron content which is measured in the interventricular septum. A value of 20 ms is considered to be the threshold for myocardial siderosis, whereas T2* values below 10 ms indicate severe myocardial iron overload [16].

**Management**

During hospital stay, after unsuccessful attempt of pharmacological cardioversion, sinus rhythm was successfully restored by synchronized electrical cardioversion. Patient underwent the procedure without complications. There was no recurrence of the arrhythmia.

Although the patient was a C282Y mutation carrier, his TS was 47.8% and ferritin value was greater than 200 ng/mL, which prompted the further diagnostic process of iron overload. He presented as well echocardiographic image consistent with hypertrophic cardiomyopathy, AF and conduction system abnormality which could be related to IC. For differential diagnosis we considered non-obstructive HCM and IC in the course of HH. Taking into consideration the fact that the patient didn’t present with other signs and symptoms related to systemic iron overload it seemed that there was a low chance of having IC, however his TS and ferritin values were elevated. Therefore, further evaluation was carried out with usage of CMR with T2* relaxometry. The study did not reveal cardiac iron overload, with T2* values above 20ms. CMR showed characteristics of hypertrophic cardiomyopathy.

In patients with HCM it is important to assess the risk of sudden cardiac death (SCD) and indications for implantation of automatic cardioverter-defibrillator (ICD) for primary prevention of SCD. In order to do that we performed ECG Holter monitoring for 48 hours, which did not demonstrate any significant ventricular arrhythmias. Calculated according to ESC Guidelines, 5-year risk of SCD was 3.2%, therefore there were no indications for ICD implantation [18,19]. Patient was discharged home in good general condition without symptoms. He was referred to outpatient Cardiology and Hepatology Clinic for long term follow up. At this point CMR didn’t show cardiac iron overload however, it is uncertain if he will develop systemic iron overload over time.

Heterozygotes for the C282Y mutation of the HFE gene usually do not express a hemochromatosis phenotype, however there are known cases of iron overload in this group of patients. It may occur in the presence of acquired factors or predisposing genetic characteristics. Therefore it seems crucial to closely monitor those patients for any symptoms that may be early manifestation of hemochromatosis development. The onset of cardiac symptoms should draw attention to possibility of IC occurrence even in heterozygotes.

**References**

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