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Genetically Associated Hypertrophic Cardiomyopathy Combined with Persistent Left Superior Vena Cava

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Abstract
Background: Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiomyopathy. The cause of HCMP can also be hereditary. An implantable cardioverter defibrillator (ICD) is an efficient way of preventing sudden cardiac death in these patients.
Aim: Diagnosis and treatment ofgenetically associated hypertrophic cardiomyopathy.
Case Report: We present a 28-year patient with a history of tachycardia, dizziness, transient chest pains and anamnestic information on episodes of short-term loss of consciousness and fatigue. She has a positive family history of HCM and her uncle died young from sudden cardiac death (SCD). The electrocardiogram showed hypertrophy, which was confirmed with echocardiography and MRI. Genetic testing confirms PRKAG2 gene mutation. Holter24-hour ECG monitoring showed domination of sinus bradycardia after which it was recommended implantation of ICD. On implantation, persistent left superior vena cava (PLSVC) was discovered and the implantation side was changed. A bipolar Implantable Cardioverter Defibrillator was implanted.
Conclusion: When HCM is confirmed at a young age, genetically associated HCM should always be considered. Early recognition of hereditary hypertrophic cardiomyopathy can facilitate better disease management and follow-up even before symptoms appear.

Keywords: hypertrophic cardiomyopathy, PRKAG2 gene mutation, PLSVC, SCD, ICD.

Introduction

Hypertrophic cardiomyopathy has a prevalence of approximately 0.2% and is the most frequently inherited disease of the myocardium. The diagnosis of HCM is often delayed, despite the development of new diagnostic tests (1).

In 60% of patients with HCM, the disease is caused by autosomal dominant transmission caused by a mutation in cardiac sarcomere protein genes, 5-10% have genetic inherited chromosomal abnormalities, genetic syndromes, metabolic and neuromuscular disease and the rest have non-genetic disorders like amyloidosis. To this day, several genetic mutations are known that cause hypertrophic cardiomyopathy, for example, the mutation in four-and-half LIM domain-1 (FHL-1), lysosome-associated membrane protein 2 (LAMP-2), beta-myosin heavy chain gene (MYH7), myosin-binding protein C (MYBPC3), cardiac troponin I and T gene (TNNI3, TNNT2), myosin light chain 3 (MYL3), tropomyosin alpha-1 chain (TPM1), α-actin (ACTC) etc (1, 2).

Metabolic disorders account for a greater proportion of HCM in children and adolescents. One of the most common metabolic diseases is a mutation in the gene encoding the γ_2 sub-unit of the adenosine monophosphate-activated protein kinase (PRKAG2) as is the case with our patient whom we will now present to you (3).

Case report

We present our case of a 28-year-old young female patient with a history of bradycardia, dizziness, occasionally transient chest pains, episodes of short-term loss of consciousness and fatigue over several years.

She has echocardiography six years ago with moderate concentric left ventricular hypertrophy. The patient gave information that has a positive family history of heart disease, i.e. her father and uncle have HCM and her uncle died young from sudden cardiac death.
The ECG showed changes that were in favor of hypertrophy (fulfilled voltage criteria for left ventricular hypertrophy) and shortened PR interval. The new echocardiography complements the old findings and confirms the suspicion of Non-compaction CMP (Figure 1).

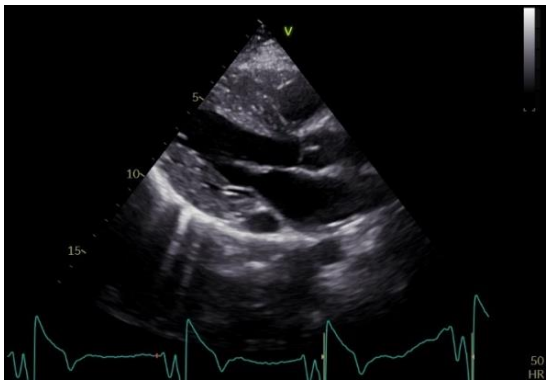

Figure 1. Parasternal long-axis echocardiography view of Non-compaction CMP

The patient is referred for genetic testing, which is done and detected a mutation of the PRKAG2 gene. 24-hour rhythm Holter monitoring shows a rhythm originating from the sinus node, shortened PR interval, signs of LVH convex elevation of the ST segment as well as deeply inverted T waves diffuse. A significant finding on the rhythm Holter monitoring was that it dominates sinus bradycardia down to 36 beats per minute.

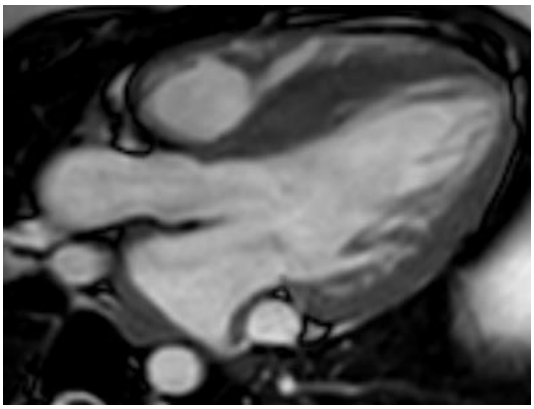

Figure2. Cardiac MRI of Non-compaction CMP

The patient was advised to get an MRI of the heart (Figure2). Cardiac MRI showed mild hypertrophy of the left ventricle with the largest measured diameter of the interventricular septum in the mid-segment 12 mm, with trabeculated myocardium in the lateral wall and apical segments of the left ventricle with a ratio of non-compact-to-compact-myocardium 2.7 (noncompaction is defined as a ratio of NC/C on end-diastole > 2.3) and normal systolic function. The finding of thickening of the papillary muscles and thin interatrial septum in the region of the fossa ovalis is also indicated, while the rest of the septum is thickened, as well as irregular thickening of the wall of the right atrium. The MRI findings of the heart are characteristic of HCM, but due to the visible trabeculations in the left ventricle, the MRI is mostly in favor of non-compact cardiomyopathy with preserved systolic function.
Because of positive genetic testing and investigations but also supported by a positive family history, a diagnosis of genetically associated noncompact hypertrophic cardiomyopathy was made.

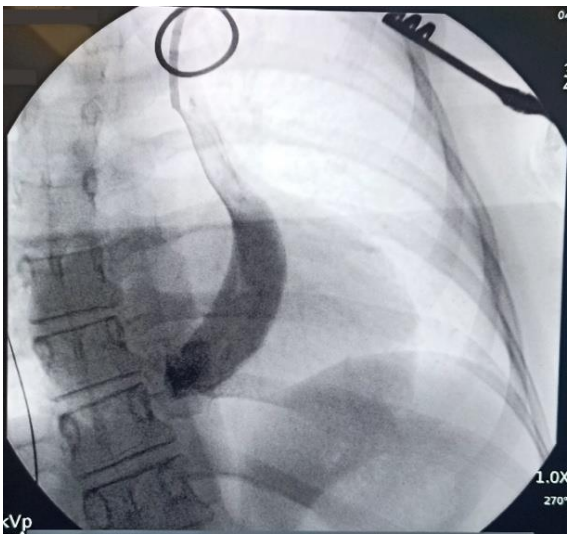

Figure3. Venogram of PLSVC

Due to the finding of persistent bradycardia and according to clinical presentation, as well as a family risk for sudden cardiac death, the decision to recommend ICD was made. At the time of the procedure, it was approached through the left side (through v.subclavia lateralis sinister), but the electrode could not be placed and persistent left superior vena cava (PLSVC) was discovered and verified radiographically with contrast after which the procedure was aborted (Figure3).

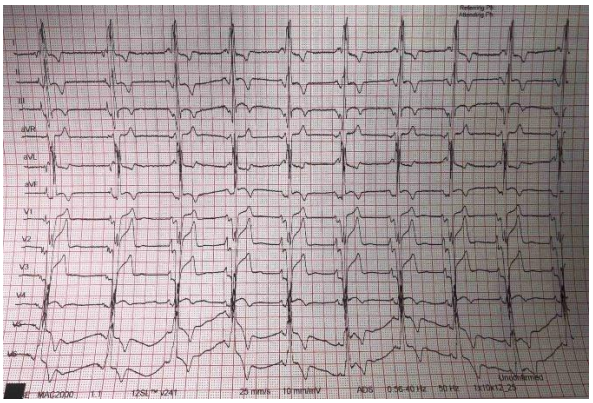

Figure 4. ECG on discharge after ICD implantation

Then the implantation was made through the right side. A Bipolar Implantable Cardioverter Defibrillator (ICD) was implanted in our patient, manufactured by Medtronic, model EVERA, with programmed tachytherapy for primary prevention and bradytherapy AAI⇒DDDlow rate 50/min (minimal V pace) and adequate stimulation of the ICD verified by ECG (Figure 4). She was discharged in a stable cardiac condition and a recommendation for further regular cardiac controls.

Discussion

In our case, the PRKAG2 gene was detected, which is located in chromosome 7 and encodes a part of the enzyme AMP activating protein kinase (AMPK), which plays a role in responding to the energy demands of cells. The enzyme is active in many tissues including cardiac and skeletal muscle. Studies suggest that AMPK may also play a role in the control and activity of other genes, as well as in regulating the activity of other ion channels in the heart (4). These channels that transport positively charged atoms in and out of heart muscle cells play a major role in maintaining normal heart rhythm. In this context, A. Axelsson's research concludes that people with a mutation in the PRKAG2 gene as we explained above, have up to 20% risk of sudden cardiac death before the age of 40, which in our case we could connect it with the anamnestic data about the premature SCD of the uncle of the patient we discuss in this paper. The author also points out that atrial fibrillation occurs in these patients at a very early age, which emphasizes the need for regular monitoring and

electrophysiological assessment in patients in whom this genetic mutation has been detected (5). Studies confirm that mutation on the PRKAG2 gene can cause Wolff Parkinson White syndrome (WPW syndrome) but the short PR interval can be also because of excessive glycogen accumulation in myocytes (6).
In addition to this discussion, we will also mention the research by F. Domingues and the authors in which, data was collected from 27 specialized cardiology centers across Europe, including 90 patients with a proven PRKAG2 mutation, with an average age of 21years (7). The research showed that 67% of the subjects with this mutation had non-compact HCM, 19% needed implantation of a pacemaker or ICD, as shown in our case, while after 6 years of follow-up an additional 21% of the cases required implantation of a pacemaker or ICD, 14% developed heart failure and required heart failure therapy, 13% died of which 8% from SCD, and 4% received a heart transplant.InJodie Ingles and coauthor's research 265 individuals with HCM included, 52% have at least one genetic mutation. The mutation detection rate was higher in individuals with a positive family history of HCM(72%) and even higher if they have also a family history of SCD (89%). If the proband is female there are more likely to have a genetic mutation (63 vs. 45%) (8). Hannah G. van Velzen and coauthors were collecting data for the period 1985 - 2016. They analyzed 209 probands with HCM and 777 relatives. Genetic mutation was detected in 72% of probands.Genetic testing was performed on 80% of relatives, of which 43% had a genetic mutation identified. At the first screening of relatives with a confirmed genetic mutation, 30% were diagnosed with HCM, and 16% developed HCM during 7 years of follow-up. During 9 years of follow-up of relatives with HCM, 6% underwent septal reduction therapy, 16% received primary prevention ICDs, and cardiac mortality was 0.3%/year (9).
PLSVC is the most common thoracic congenital malformation. It is an isolated malformation in our case but it can be associated with atrial septal defect, single atrium, ventricular septal defect, tetralogy of Fallot, coarctation of the aorta, pulmonary stenosis and anomalous pulmonary venous return (10).
Certain inherited HCM are more prone to develop atrioventricular blocks like PRKAG2. An ICD rather than a pacemaker is recommended. For patients older than 16 years 5-year estimated risk prediction model for SCD (HCM Risk-SCD Score) is used for the recommendation of ICD. HCM RiskSCD score variables are unexplained syncope, non-sustained ventricular tachycardia, left ventricular wall thickness, LVOT gradient, age, family history of SCD, and left atrial diameter (3, 11). Guidelines also recommend screening first-degree relatives of affected probands with HCM from age 10 years.

Conclusion

When the diagnosis of HCM is confirmed at a young age, genetically associated HCM should always be considered. In individuals with LVNC, there is a 20 to 40 percent chance that genetic mutation is the cause of the disease. In patients with an established family history of HCM, the mutation detection rate was significantly higher and a positive family history of sudden cardiac death further increased this rate. Early recognition of hereditary hypertrophic cardiomyopathy can facilitate better disease management and follow-up by doctors even before symptoms appear.

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Ethical approval - The patient provided informed consent for the publication of data and images.

Declaration of authorship - AGconceived and designed the study; all authors acquired the data; all authors acquired the data analyzed and interpreted the data; all authors acquired the data drafted the manuscript; all authors acquired the data critically revised the manuscript for important intellectual content; all authors acquired the data gave approval of the version to be submitted; all authors acquired the data agree to be accountable for all aspects of the work.

Conflicts of Interest - There is no conflict of interest regarding the publication of this paper.

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