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CASE REPORT

Familial hypertrophic cardiomyopathy: A case with a new mutation in the MYBPC3 gene

Ailevi hipertrofik kardiyomiyopati: MYBPC3 geninde yeni bir mutasyon olan bir olgu

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Summary– Familial hypertrophic cardiomyopathy is a genetically heterogeneous disease with variable clinical features that is inherited as autosomal dominant with variable penetrance. Recent developments in genetics of hereditary cardiomyopathy have not only enlightened many points about pathogenesis, but have also provided great benefit to diagnostic approaches of clinicians. Heterozygous mutation of c3691-3692insTTCA in MYBPC3 gene was identified in a pediatric patient with diagnosis of hypertrophic cardiomyopathy at clinic. Hypertrophy was observed in sister and father of the patient in echocardiography screening, and it was subsequently determined that they also had same mutation. This mutation has not previously been defined and reported previously in the literature as cause of hypertrophic cardiomyopathy.

Özet– Ailesel hipertrofik kardiyomiyopati (HKM) değişken klinik özellikler gösterebilen, otozomal dominant olarak geçen eksik penetranslı ve genetik olarak heterojen bir hastalıktır. Kalıtsal kardiyomiyopatilerin genetiği ile ilgili güncel gelişmeler, bu grup hastalıkların patogenezi hakkında birçok noktanın aydınlatılmasına ek olarak özellikle klinisyenlere tanısal yaklaşımda büyük faydalar sağlamıştır. Kliniğimizde HKM ile takip edilen çocuk hastada MYBPC3 geninde heterozigot olarak c3691-3692insTTCA mutasyonu tanımlandı Hastanın kız kardeşi ve babasının ekokardiyografi taramasında hipertrofi gözlendi ve ardından aynı mutasyona sahip oldukları tespit edildi. Bu mutasyon daha önce literatürde hipertrofik kardiyomiyopati nedeni olarak tanımlanmamış ve bildirilmemiştir.

Hereditary cardiomyopathy refers to a group of diseases in which heart muscle has abnormal structure and function without any acquired factor. Prevalence of cardiomyopathy in the general population is 1/500.[1] Cardiomyopathies are subgrouped as hypertrophic, dilated, restrictive, arrhythmogenic right ventricular, and unclassified.[2] Hypertrophic cardiomyopathy is the first subgroup to have molecular mechanisms studied, and the only one to have molecular diagnostic test.

Abbreviations:

β-MHC	*Beta-myosin heavy chain*
ECG	*Electrocardiography*
ECHO	*Echocardiographic*

Hypertrophic cardiomyopathy is a primary cardiac muscle disease without conditions increasing load on the heart, such as aortic stenosis, hypertension, or hyperthyroidism, and is usually characterized by left ventricular hypertrophy. Phenotypic and genetic heterogeneity is well documented, and different genes with different rates of expression have been associated with hypertrophic cardiomyopathy. Genetic mutations in MYH7 and MYBPC3 genes are responsible for about 80% of cases.[3] Asymptomatic first-degree relatives of patients with hypertrophic cardiomyopathy who have mutation should be screened for mutation as well. Presently described is case of a family with hypertrophic cardiomyopathy in whom mutation in MYBPC3 gene was identified for the first time as cause of this disease.

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CASE REPORT

A 2-year-old male patient who had been in follow-up since neonatal period with diagnosis of hypertrophic cardiomyopathy and small muscular ventricular septal defect was presented at clinic. Physical examination revealed blood pressure was 90/50 mmHg and heart rate was 100/bpm and regular. On cardiac auscultation, 3/6 pansystolic murmur was detected in mesocardiac area. There was no abnormality found in examination of other systems. Cardiothoracic ratio was normal on telecardiography. Electrocardiography (ECG) was appropriate for his age. Echocardiographic (ECHO) examination revealed increased left ventricular wall thickness without left ventricular outflow tract stenosis or coarctation of aorta. End diastolic interventricular septum thickness was measured at 6.8 mm (N: 2.1–4.7) and posterior wall thickness of the left ventricle at 4.3mm (N: 1.9–3.5) (Figure 1). There was no accompanying dysmorphic feature.

Parents were not consanguineous, and there was no history of sudden cardiac death in the family. Initial screening revealed that despite being asymptomatic, the father and sister of the patient had ECHO results that were consistent with hypertrophic cardiomyopathy. Both had increased wall thickness of interventricular septum and posterior of left ventricle, according to age and gender, but systolic and diastolic functions and rhythm were normal on ECG. Metabolic screening tests of the patient for etiology of hypertrophic cardiomyopathy were normal, and so consultation with genetics clinic was arranged. Chromosome analysis of the patient was reported as normal karyotype. Analysis for the entire gene sequence of MYBPC3 and MYH7 genes was performed as suggested in the Online Mendelian Inheritance in Man with Sanger method (3130XL Genetic Analyzer; Applied Biosystems, Inc., Foster City, CA, USA) for etiology of hypertrophic cardiomyopathy.[4] As a result of the analysis, while no mutation in MYH7 gene was detected, heterozygous mutation of c3691-3692insTTCA in MYBPC gene was found, which has not been mentioned in the literature before as cause of hypertrophic cardiomyopathy (Figure 2). Additional family screening was performed due to the outcome of in silico analysis (Sorting Tolerant From Intolerant [SIFT], http://sift.jcvi.org and Mutation Taster; http://www.mutationtaster.org), since mutation found was considered to be highly probable cause of disease. MYBPC3 gene was examined in the family members, and same mutation was found in the other members of the family with hypertrophic cardiomyopathy (Figure 3). Genetic variant detected in this family was located at the 32nd exon of the genome and was found to cause damage to the structure and the function of protein in the in silica analyses. As a result, 2-year-old patient, the index case, continues to be monitored with regular ECHO screening. Written informed consent for publication was provided by the family.

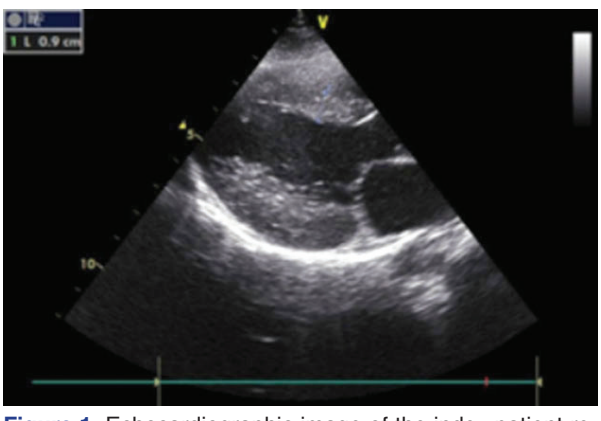

Figure 1. Echocardiographic image of the index patient revealing hypertrophy of the interventricular septum and posterior wall of the left ventricle.

DISCUSSION

Hypertrophic cardiomyopathies are familial in approximately 55% of cases.[5] Familial hypertrophic cardiomyopathy is a primary disease of the heart muscle, with variable penetrance and autosomal dominant inheritance. Thus far, more than 1400 mutations in some 13 or more different genes have been identified that cause the disease, the majority of which are missense mutations. These mutations are in sarcomere or sarcomere-associated protein, cardiac β-myosin heavy chain (β-MHC), myosin binding protein C, cardiac troponin T, tropomyosin, troponin I, basic or regulatory light chain myosin, and the genes encoding titin and actinin-2 molecules.[3] Cardiac β-MHC gene (MYH7) mutation was found in approximately 15% to 30% of hypertrophic cardiomyopathies in extensive genetic screening.[6] Furthermore, this gene is associated with more serious disease, increased hypertrophy, being symptomatic at an earlier age, and poor prognosis.[6]

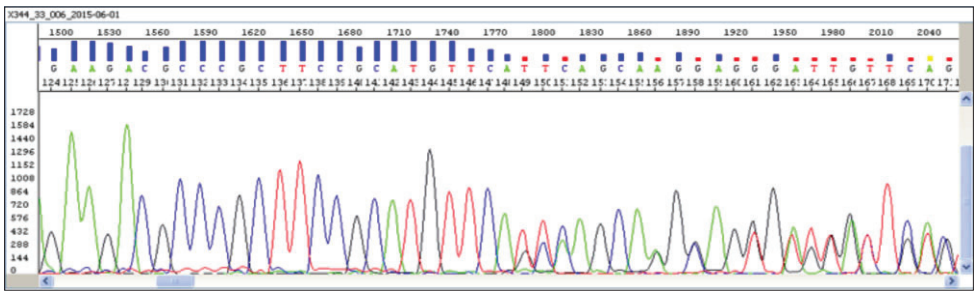

Figure 2. Image of the MYBPC3 gene sequence analysis of the patient.

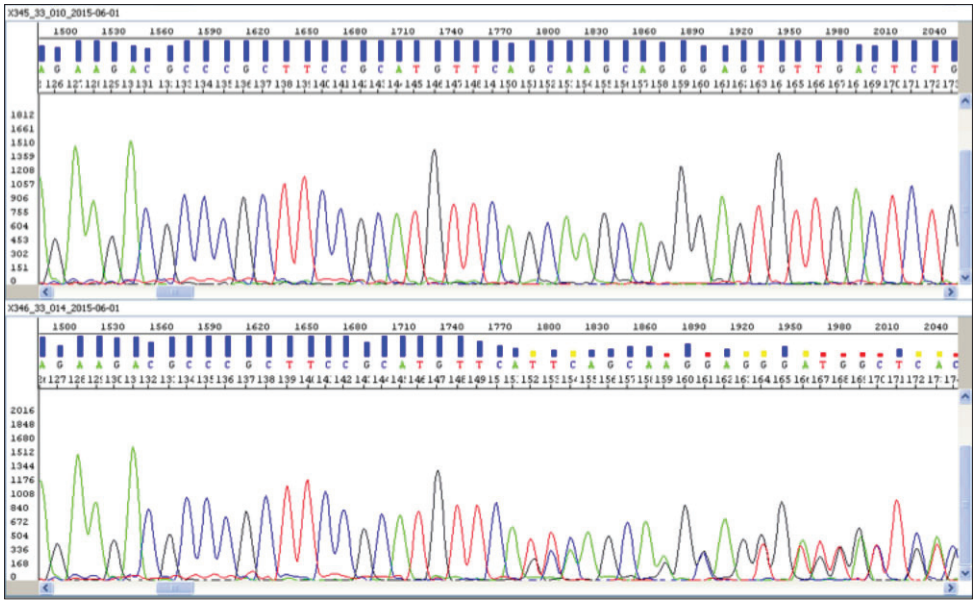

Figure 3. Images of the MYBPC3 gene sequence analysis of the father and sister of the patient.

In Turkey, in a study investigating gene mutations of families with hypertrophic cardiomyopathy, missense mutation in the gene of MYH7 (403Arg→Gln) was positive in 25% of clinically symptomatic patients and in 2% of phenotype-negative relatives of these patients.[7] Therefore, family screening is recommended when there is an index case, such as presently described.

Mean age of the appearance of left ventricular hypertrophy and clinical features is thought to be related to differences in expression of the responsible gene and mutation, as well as environmental factors and other genetic factors.[8]

Patients with hypertrophic cardiomyopathy may be asymptomatic or may show a variety of clinical signs, ranging from mild symptoms due to heart failure to sudden cardiac death. Hypertrophic cardiomyopathy is often the underlying cause of sudden cardiac death before the age of 35.[3] However, it is not possible to say with current knowledge how often the cause of sudden cardiac death in childhood is cardiomyopathy.[2] Though symptoms vary among individuals, chest pain; pulmonary congestion symptoms, such as dyspnea, orthopnea, or paroxysmal nocturnal dyspnea; syncope; and palpitations are often seen in older children and adults.[3]

Presence of such symptoms as left ventricular wall thickness ≥30mm, family history of sudden cardiac death, cardiac arrest/ventricular tachycardia, recorded intermittent ventricular tachycardia (≥3 consecutive beats with ≥120 heart rate), or unexplained syncope are not only major risk factors for sudden cardiac death, but are also associated with high rate of sudden death.[3]

Treatment of hypertrophic cardiomyopathy varies depending on the status of the disease. Follow-up without treatment, lifestyle changes (avoiding sports), medications (calcium channel blockers, beta-blockers, diuretics), septal myotomy, inserting a dual-chamber pacemaker, and alcohol ablation of septal myocardium are treatment modalities that may be applied. Intracardiac devices, in particular, have been used in recent years to prevent sudden death. These devices have been determined to be superior to inhibitory drugs such as beta-blockers and amiodarone in prevention of sudden cardiac death.[3] Our patient is still followed up without medication since there is lack of symptoms.

Asymptomatic first-degree relatives of patients with hypertrophic cardiomyopathy should undergo molecular screening. In addition, they should be evaluated by a cardiologist based on minimum of history, physical examination, ECG, and transthoracic ECHO.

Screening is recommended once every 3 to 5 years for the first decade, annually for ages 12 to 18 years or athletes, and every 5 years for others until adulthood. The present case emphasizes the importance of screening for hypertrophic cardiomyopathy for early diagnosis, treatment, and determination of follow-up program, even in patients who are asymptomatic or have mild symptoms, or have no family history. Mutation-specific tests should be performed if the mutation causing the disease is known. Genes that may be a factor should be investigated using appropriate molecular genetics methods and proper screening algorithm.

Conflict-of-interest: None declared.

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Anahtar sözcükler: Ekokardiyografi; hipertrofik kardiyomiyopati; moleküler genetik; MYBPC.