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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 which has variable clinical features and inherited as autosomal dominant with incomplete penetrance. Recent developments on the genetics of hereditary cardiomyopathy, not only enligthened many points about the pathogenesis, but also had a great benefit in the diagnostic approaches of clinicians. In a pediatric patient with the diagnosis of hypertrophic cardiomyopathy a heterozygous mutation of c3691-3692insTTCA in MYBPC3 gene was identified in our clinic. Sister and father of the patient who had hypertrophy in echocardiography screening were determined that the same mutation also. This mutation was not defined and reported previously in the literature and thought to cause the disease because of leading to the frame shift, thus worth to be presented.

Özet– Ailesel hipertrofik kardiyomiyopati (HKM) klinik özellikleri değişken olabilen, otozomal dominant olarak kalıtılan 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 pediatrik bir hastada MYBPC3 geninde heterozigot olarak c3691-3692insTTCA mutasyonu tanımlandı. Hastanın ekokardiyografide hipertrofi saptanan kız kardeşi ve babasında da aynı mutasyon olduğu belirlendi. Bu mutasyon, daha önce tanımlanmamış bir mutasyon olmakla birlikte çerçeve kaymasına neden olmasından dolayı hastalığa yol açabileceği düşünülmüş ve literatürde daha önce bildirilmediği için sunulmaya değer görülmüştür.

Hereditary cardiomyopathy refers to a group of diseases that have abnormal structure and function of the heart muscle without any acquired factor. The prevalence of the 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 studied subgroup of them with the molecular mechanisms and the only one having molecular diagnostic test.

Hypertrophic cardiomyopathy is a primary cardiac muscle disease without the conditions increasing after load of the heart such as aortic stenosis, hypertension or hyperthyroidism and usually characterized by left ventricular hypertrophy. Phenotypic and genetic heterogeneity is well documented and different genes with different rate 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 the patients with hypertrophic cardiomyopathy, who have the mutation, should absolutely be screened for detected mutations. In this article a family has presented with hypertrophic cardiomyopathy having a mutation that is identified in MYBPC3 gene for the first time which is known to cause this disease.

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CASE REPORT

Two-year-old male patient have been followed since neonatal period with the diagnosis of hypertrophic cardiomyopathy and small muscular ventricular septal defect. In physical examination blood pressure was 90/50 mmHg; heart rate was 100/min and regular. In cardiac auscultation 3/6 pansystolic murmur was detected on the mesocardiac area. There was not any abnormality in examination of other systems. Cardiothoracic ratio was normal on telecardiography. ECG was appropriate for his age. In echocardiographic (ECHO) examination increased left ventricular wall thickness was present without left ventricular outflow tract stenosis and coarctation of aorta. End diastolic interventricular septum thickness were detected (IVSd) as 6.8 mm (N: 2.1-4.7) and posterior wall thickness of the left ventricle as (LVPWd) 4.3 mm (N: 1.9-3.5) (Fig. 1). There was no accompanying dysmorphic feature.

Parents were not relatives and also there was not history of sudden cardiac death in the family. Despite being asymptomatic, ECHO results of the father and sister of the patient were consistent with the hypertrophic cardiomyopathy in the family screening. Both had increased wall thickness of interventricular septum and posterior of left ventricle according to age and gender, but systolic and diastolic functions and also rhythm were normal in ECG. Metabolic screening tests of the patient for the etiology of hypertrophic cardiomyopathy were normal and so patient consulted to the genetics clinic. The chromosome analysis of the patient was reported as normal karyotype. Analysis for the entire gene sequence of MYBPC3 and MYH7 genes were performed as suggested in OMIM by Sanger method (3130XL, Applied Biosystems) for the 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 did not mentioned in the literature before (Fig. 2). Moreover, family screening was performed due to the outcome of the silico analysis (SIFT and Mutation Taster), since the mutation which found was considered as highly probable to cause the disease. The written informed consent for the publication of the patient and his family obtained and then, the MYBPC3 gene was examined in the family scanning and the same mutation was found in all other affected members of the family also (Fig. 3). The genetic variant detected in this family was located at the 32nd exon of the genome and was found to cause damage on the structure and the function of the protein in silica analyzes. As a consequence, 2 -year-old patient, the index case, has still been followed with ECHO screening regularly.

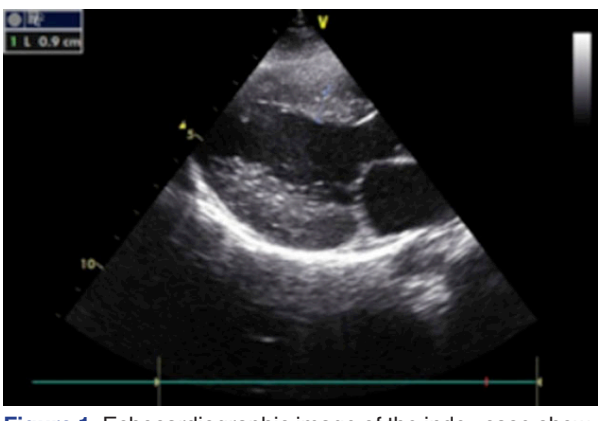

Figure 1. Echocardiographic image of the index case showing hypertrophy of interventricular septum and posterior wall of left ventricle.

DISCUSSION

Hypertrophic cardiomyopathies are familial approximately 55% of the cases.[5] Familial hypertrophic cardiomyopathy is a primary disease of the heart muscle with variable penetrance and autosomal dominant inheritance. So far, more than 1,400 mutations at least in 13 different genes that cause the disease has been identified the majority of which is missense. These mutations are in sarcomere or sarcomere-associated protein, cardiac β-myosin heavy chain, 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 beta-myosin heavy chain (β-MHC) gene (MYH7) mutation was found in approximately 15 to 30% of hypertrophic cardiomyopathies in extensive genetic screenings.[6] Furthermore, this gene is associated with more serious disease, increased hypertrophy, being symptomatic at an earlier age and poor prognosis also.[6]

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

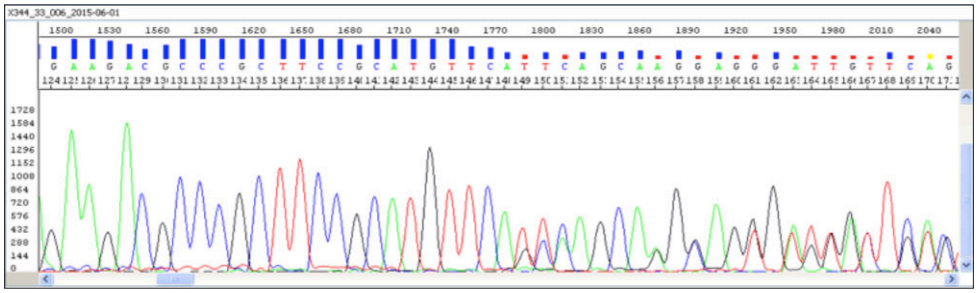

Figure 2. Images of the MYBPC3 gene sequence analysis of the patient.

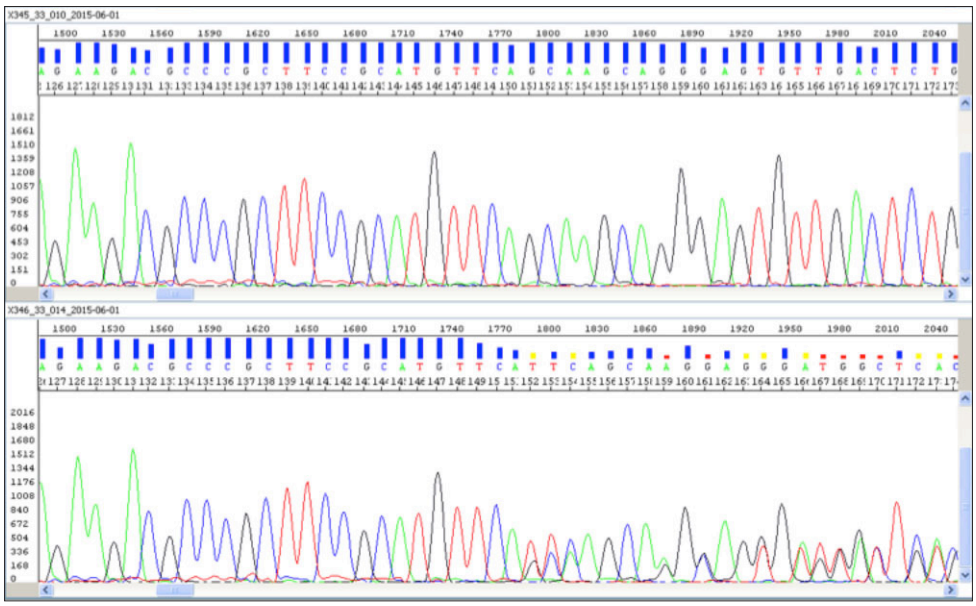

Figure 3. Images of the MYBPC3 gene sequence analysis of the father and sister of the patient.

The mean age of the appearance of left ventricular hypertrophy and the clinical features are thought to be related to the expression differences of the responsible gene and mutation, and also environmental factors and other genetic factors.[8]

Patients with hypertrophic cardiomyopathy can even be asymptomatic or may show a variety of clinical signs ranging from mild symptoms due to heart failure to the 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 that the cause of the sudden cardiac death is often cardiomyopathy for childhood.[2] Even though, symptoms vary in individuals, chest pain, pulmonary congestion symptoms such as dyspnea, orthopnea, paroxysmal nocturnal dyspnea, syncope, loss of consciousness 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 (≥3beat, ≥120 heart rate), unexplained syncope are not only major risk factors for sudden cardiac death but also is associated with a high rate of sudden death.[3]

Treatment of hypertrophic cardiomyopathy varies depending on the status of the disease. Follow-up without treatment, lifestyle changes (to avoid compulsive sports), medications (calcium channel blockers, beta-blockers, diuretics), septal myotomy, inserting a dual-chamber pacemaker, alcohol ablation of septal myocardium are treatment modalities which applied. Especially intracardiac devices are used in recent

years that can prevent sudden death. Intracardiac devices were determined to be superior to the inhibitory drugs such as beta-blockers and amiodarone in prevention of sudden cardiac death.[3] Our patient is still followed up without medication since lack of symptoms.

Asymptomatic first degree relatives of patients with hypertrophic cardiomyopathy should be screened as molecularly. In addition they should be evaluated by a cardiologist at least via history, physical examination, ECG and transthoracic ECHO.

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

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