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RESEARCH ARTICLE

Jak2 gene mutations seems not to play a role in the etiology of hypertrophic cardiomyopathy; cross-sectional, observational study

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ABSTRACT

Objective: Hypertrophic Cardiomyopathy (HCMP) is characterized with uncontrolled and severe hypertrophy of left ventricle without any determined underlying reason. The mechanisms causing myocardial hypertrophy are still not fully understood. In the literature there are some data with animal studies about Jak/STAT signal pathway may be related to myocardial hypertrophy. This study aimed to surrogate the Jak mutations in patients with HCMP.

Methods: The study included 26 patients with HCMP that were under management and monitorization of Adnan Menderes University cardiology out patient clinic. Blood samples were taken into collecting tubes with EDTA and with the help of DNA isolation kit, total genomic DNA was isolated and related exons were amplified with the PCR method. After PCR, sequence of nucleotids were analysed with the DNA sequence analysis system.

Results: 11 woman and 15 male HCMP patients were included to the study (the median age was 52,2±12,5) 19 of them have septal, 3 of them have apical and 4 of them have concentric type LVH. 14 of them have gradient in left ventricular outflow tract.13 of them have familial history of HCMP. 22 of them have sinus rhythm and 4 of them have paroxysmal atrial fibrillation. At the end of the study Jak2 gene mutations were not determined in any of our 26 HCMP patients.

Conclusion: The limitation of our study was relatively small number of patients. The confirmation of data with randomised bigger studies is needed. Our relatively small data is suggesting that there may be no relation with HCMP and Jak2 mutations.

Keywords: Hypertrophy, Hypertrophic Cardiomyopathy, Jak 2 Mutations, Left Ventricle

ÖZET

Jak2 gen mutasyonları hipertrofik kardiyomiyopati etiyolojisinde rol oynamıyor; kesitsel, gözlemsel bir çalışma

Amaç: Hipertrofik Kardiyomiyopati (HKMP) altta yatan herhangi bir neden olmaksızın ortaya çıkan sol ventrikülün kontrolsüz ve ciddi hipertrofisi ile karakterizedir. Miyokardiyal hipertrofiye yol açan mekanizmalar halen tam olarak anlaşılamamıştır. Literatürde Jak/Stat sinyal yolağının miyokard hipertrofisi ile ilgili olabileceğine dair hayvan çalışmaları bulunmaktadır. Bu çalışma HKMP'si olan hastalarda Jak mutasyonlarının rolünü araştırmayı hedeflemektedir.

Yöntem: Çalışma Adnan Menderes Üniversitesi Tıp Fakültesi kardiyoloji polikliniğince takip ve tedavi edilen 26 HKMP hastası ile yapılmıştır. Kan örnekleri EDTA içeren tüplere alınarak, DNA izolasyon kiti yardımıyla total DNA genomu izole edilmiş ve ilgili ekzonlar PCR metoduyla amplifiye edilmiştir. PCR sonrası nükleotid dizileri DNA dizi analiz sistemi yardımıyla analiz edilmiştir.

Bulgular: 11 kadın ve 15 erkek HKMP hastası çalışmaya dahil edilmiştir (ortalama yaş 52,2±12,5). Hastaların 19'unda septal, 3 'ünde apikal, 4'ünde konsantrik sol ventrikül hipertrofisi mevcuttu. 14'ünde sol ventrikül çıkış yolunda gradiyent saptandı. 13'nün ailesel geçiş öyküsü mevcuttu. 22'si sinüs ritmindeydi ve 4'ünde paroksismal atriyal fibrilasyon mevcuttu. Sonuçta 26 hastanın hiçbirisinde Jak2 gen mutasyonu saptanmadı.

Sonuç: Çalışmamızın kısıtlılığı rölatif olarak küçük sayıdaki hasta popülasyonudur. Çalışmamızın verilerinin daha büyük randomize çalışmalar ile desteklenmesi gerekir. Çalışmamıza ait kısıtlı veri HKMP ile Jak2 mutasyonları arasında anlamlı bir ilişki olmayabileceğine işaret etmektedir.

Anahtar kelimeler: Hipertrofi, Hipertrofik kardiyomiyopati, Jak 2 Mutasyonları, Sol ventrikül

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INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is characterized by excessive left ventricular hypertrophy without underlying prominent reason. It may be sporadic or familial and may have heterogeneous phenotypes [1]. Broad spectrum of genetic mutations were demonstrated and genetic studies are still going on with the hope to highligth undiscovered ways for novel theareupotic approaches [2,3].

When there is no causative genetical anomaly, cardiac hypertrophy (CH) it self is a natural defense to cope with some pathological circumstances [4]. CH involves many biological pathways and cardiothropin-1 is regarded to play an important role in that process. Cardiotrophin-1 is a member of interleukin-6 cytokin family and known to be a potent activator of CH [5]. It leads to CH by activating Jak2 and causes increased activation of angiotensinogen gene through STAT3 pathway [5,6]. Related kinase Jak2 is a member of the Janus family of non-receptor tyrosine kinases and seems to have the most important role in the regulation of that pathway [7,8,9]. It plays a pivotal role in the regulation of cardiovascular system as well as physiological processes and cellular stress responses [8,9]. The circumstances to cause stimuli of CH, like acute pressure overload, was also demonstrated to activate Jak2 which in turn leads to secretion of angiotensin II [8,9]. There are some animal studies as well as case reports to call attention on the association between Jak2 mutations and HCMP [10,11). Of interest, Gattenlohner et al. reported a patient with cardiac Jak2 mutation V617F causing both hypertrophic cardiomyopathy and myeloproliferative disease [11].

The data is drawing attention to Jak2 that it may be realated to broad spectrum of diseases including the cardiovascular system. Considering its close relation with the CH pathways, we hypothesized that the mutations of Jak2 may be related to HCM.

MATERIALS and METHODS

This research was designed as a cross-sectional, observational study and included 26 patients with hypertrophic cardiomyopathy (HCMP) who were under management and monitoring at the Adnan Menderes University Cardiology Outpatient Clinic. The diagnosis of HCMP was compatible with the related guideline of ESC [12]. Definition requires the exclusion of pathologies such as hypertension, aortic valve stenosis, subvaortic membrane and systemic diseases which could cause left ventricular hypertrophy. After the exclusion, HCMP is defined as the presence of hypertrophic (wall thickness ≥15 mm) but not dilated left ventricle assessed with 2-D echocardiography [12].

Transthoracic echocardiography was performed using Philips HD-11XE utilizing standard techniques with the participants in the left lateral decubitis position as recommended in the AHA and the ESC Association Heart Cavity Measurement Guide [13]. A septal wall thickness of 1.3 cm or more is considered indicative of asymmetric septal hypertrophy [12]. Obstructive hypertrophic cardiomyopathy was identified through continuous Doppler echocardiography at rest, along with an LV outflow tract gradient of ≥ 30 mmHg. Additionally, the presence and degree of systolic anterior motion of the mitral valve were evaluated using the criteria described previously [14]. DNA was extracted from EDTA-anticoagulated peripheral blood by using MagNA pure compact Kit (Roche Diagnostics, Germany).The concentration of DNA was determined by specrophotometry using the Nanodrop 2000 spectrophotometer and was amplified by polymerase chain reaction . The polymerase chain reaction was done in a volume of 50 µl with primers (5′-TGCTGAAAGTAGGAGAAAGTGCAT-3′and5′-TCCTACAGTGTTTTCAGTTTCAA-3′, respectively) and 0.8mM deoxyribonucleotide triphosphates (dNTPs), 1,5 mM MgCI2, 1.5 U Tag polymerase (Roche), and 5 µL of 10X buffer provided by the enzyme manufacturer (Roche, Germany). The reaction was cycled 35 times between 94°C for 30 seconds, and 52°C for 40 seconds and 72°C for 40 seconds, and followed by 2 minutes at 72°C. Polymerase chain reaction (PCR) was performed to prepare the template, followed by cleaning using the QIAquick PCR purification kit for sequencing. Fluorescent dye chemistry sequencing was then carried out using the same primers, with capillary electrophoresis conducted on the ABI 3100 Prism Genetic Analyzer. For sequence analysis, the JAK2 sequence (accession NM-004972) and the corresponding region from the NC_000009 chromosome 9 contig were utilized.

RESULTS

11 woman and 15 male HCMP patients were included to the study (the median age was 52,2±12,5). Gender distribution of 26 HCM subjects were found to be 42.3% / 57.7% . The age range of all cases was determined as 20-65. 19 of them have septal, 3 of them have apical and 4 of them have concentric type LVH. 14 of them have moderate gradient in left ventricular outflow tract.13 of them have familial history of HCMP. 22 of them have sinus rhythm and 4 of them have paroxysmal atrial fibrillation. 3 patients have diabetes, 8 of them have hypertension. None of our patients have myeloproliferative blood neoplasms. Charachteristics of the study population was demonstrated in Table 1 and Table 2. At the end of the study Jak2 gene mutations were not determined in any of our 26 HCMP patients.

Systolic anterior motion was found out in 11(42.3%) of hypertrophic cardiomyopathy patients, and the gradient was detected in left ventricular outflow tract in 14(53.8%). Of the hypertrophic cardiomyopathy patients, 4 had atrial fibrillation and others had sinus rhythm. 50% of hypertrophic cardiomyopathy patients had a familial transition history. there was a history of

syncope, VT, arrest in 4 of the hypertrophic cardiomyopathy cases (15.4%).

	HCMP(n=26)
Smoking	12 (46,2%)
Alcohol	3 (11,5%)
History of DM	3 (11,5%)
History of HT	8(30,7%)
History of CAD	1 (3,8%)
BBdrug	19 (73,1%)
ACE inhibitor	6 (23,1%)
ARB	4 (15,4%)
CCB	6 (23,1%)
Diuretics	7 (26,9%)
Antithrombotic drugs	12 (46,2%)
Statins	1 (3,8%)
Abbreviations: DM: Diabetes Mellitus, CAD: Coronary artery disease, BB: Beta blocker, ACE inhibitor: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker, CCB: Calcium channel blocker, HCMP: Hypertrophic Cardiomyopathy	

Table 1: Drug use and risk factors of the cases

Septal type HCMP	19 (73,1%)
Apical type HCMP	3 (11,5%)
Concentric type HCMP	4 (15,4%)
Moderate Gradient in LVOT	14(53,8%)
Atrial Fibrillation	4 (15,4%)
Sinus Ryhthm	22(84,6%)
Familial History of HCMP	13(50%)
SAM of mitral valve	11(42,3%)
History of Syncope/VT/Arrest.	4(15,4%)
Abbreviations: HCMP: Hypertrophic Cardiomyopathy, LVOT: Left ventricular outflow tract , SAM: Systolic anterior motion of mitral valve, VT: Ventricular tachycardia	

Table 2: Characteristics of the HCMP patients

DISCUSSION

In this particular study we demonstrated that Jak2 gene mutations may not play a major role in the etiology of HCMP disease.

Previous reports about the relation between Jak2 mutations with CH were drawing attention. Shi et al, demonstrated association between CH and myeloproliferative neoplasms in JAK2V617F transgenic mice [10]. They suggested that JAK2V617F-induced blood disorders have a major impact on heart function and lead to CH. Zhao et al. also suggested that stachydrine mitigates isoproterenol-induced CH and fibrosis by suppressing inflammation and oxidative stress, which occurs through the inhibition of NF-κB and JAK/STAT signaling pathways in rats [15]. They took attention on the close relation betweeen the Jak/STAT pathway and the CH. Of interest, Gan et al. reported that rats with a cardiac-specific deletion of Jak2 has myocardial hypertrophic remodeling and impaired left ventricular function [16]. They showed that the defective cardiac function of the specific deletion of cardiac Jak2 in rats was associated with altered protein levels of sarcoplasmic reticulum calcium-regulatory proteins. Finally Starksen et al. previously reported that cardiac myocte hypertrophy is associated with c-myc protooncogene expression [17]; where Jak2 plays a crucial role in the induction of c-myc by Bcr-abl and once more somehow getting involved in the CH pathways [18].

However, in contrast with the data taking attention on the possible association of Jak2 and CH, we couldn't find any significant relation between Jak2 mutation and the CH of HCMP patients in our study popülation.

We hypothesized that Jak2 may play a role in HCMP etiology and could not find association betweeen Jak2 mutations and the disease. This result may represent a negative relation between two disease. On the other hand, patients with Jak2 mutations may represent a very small number of group in the popülation of HCMP patients and our study population may not be enough to demonstrate the relation. The limitation of our study is its relatively small number. Our results should be confirmed with a randomised bigger studies. Our negative result also may point to a different perspective. Future studies may work on the status of CH (instead of HCMP) and impairment of left ventricular function in patients with Jak2 mutations.

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Data availibity statement : The data that support the findings of this study are available from the corresponding author upon reasonable request.

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