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The frequency of diastolic dysfunction in patients with sarcoidosis and it's relationship with HLA DRB1* alleles

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Abstract. *Background:* Impaired systolic function is common in sarcoidosis however the frequency of diastolic dysfunction (DD) and it's possible genetic basis has not been fully elucidated yet. The aim of this study is to evaluate the frequency of left ventricular DD(LVDD) and right ventricular DD(RVDD) and it's possible relationship between Human Leukocyte Antigen(HLA)-DRB1* alleles in patients with sarcoidosis. *Methods:* Seventy seven patients (51 females, mean age 41.1±8.2yrs) without known sarcoid related or any other structured heart disease and 77 healthy controls with a similar age and gender (38.7±7.8yrs,51 females) were included in the case control study. DD was diagnosed with echocardiography. RVDD was defined as early(E)/late(A) ratio<1 or >2 on tricuspit valve. LVDD was defined as E/A ratio<1 or >2 on mitral valve, with isovolumetric relaxation time(IVRT)>90 miliseconds(msn) or deceleration rate of early diastolic flow(Edec)>220msn respectively. All patients were HLAtyped with the Sequence Specific Oligonucleotide Probe(SSOP) method. *Results:* The frequencies of LVDDs and RVDDs were significantly higher in sarcoidosis patients than the controls (26.0% vs. 2.6% for LVDD; and 42.9% vs. 18.2% for RVDD)($p<0.05$). No significant difference was found in patients according to the presence of RVDD and LVDD in terms of age, gender or respiratory function test parameters. Although the frequency of HLA DRB1* alleles were comparable among patients with RVDD, HLA DRB1*14 alleles were more frequent in patients with LVDD. *Conclusions:* Biventricular DD is common in patients with sarcoidosis without manifest cardiac involvement. HLA DRB1*14 allele seems to be related with LVDD in this study population. *(Sarcoidosis Vasc Diffuse Lung Dis 2019; 36 (4): 285-293)*

Key words: sarcoidosis, echocardiography, HLA alleles, diastolic dysfunction

1. Introduction

Sarcoidosis is a multisystemic chronic granulomatous disease of unknown origin. The most common site of involvement is lung with lymph nodes but it can affect any organ system. Although the exact immunopathogenesis is still scarce, an important aspect in granuloma formation is the activation of T cells by antigen-presenting cells through a molecular interaction of the T-cell receptors and antigen-presenting molecules which are genetically encoded in the HLA region (1). HLA Class II molecules are the key elements between the antigen presenting cell which process the antigen and the T- cell receptors. Therefore, the crucial event in the pathogenesis of sarcoidosis seems to be the orchestration between

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the antigen, HLA Class II molecules and T-cell receptors in the genetically susceptible host (2).

Cardiac involvement is a potentially life threating condition in sarcoidosis. Several reports estimated that up to 5% of patients clinically manifest cardiac involvement however recent research with new technology revealed higher prevelance rates; at least 25%, with significant variability in different ethnic groups (3-6). Cardiac involvement may range from silent myocardial granulomas to symptomatic conduction disturbances, ventricular arrhythmias, progressive heart failure, and sudden death which accounts for 13-25% of disease-related deaths in the United States and much more higher in Japan (6, 7). Any portion of the heart can be regionally infiltrated by sarcoid granulomas but the myocardium is the most frequently involved site mostly in the ventricular septum (32%) and left ventricle inferior wall (25%) which may results in severe rhythm disturbances and those related morbidity and mortality (8).

Echocardiography, which may show systolic and diastolic function is one of the widely used basic investigational techniques in cardiac involvement. There are numerous articles investigating the relationship between left and right ventricular systolic functions and pulmonary sarcoidosis, however the data about diastolic functions are still scarce. According to a previous report, a reversed E/A Doppler ratio has been reported to be the most common echocardiographic pattern of diastolic dysfunction (DD) seen in early cardiac sarcoidosis (CS) (9).

Since the key role is the ability to recognize antigen and initiate an immune response, most of the tremendous evolution about sarcoidosis genetics focused on HLA-Class II molecules. Certain HLA-Class II alleles which influence disease course were indicated to date. Of those, HLA-DRB1-alleles confer the highest risk on the population level (10). Despite these findings, the possible effect of genetics on systemic, i.e. cardiac involvement have not been elucidated yet (4). From another point of view, several reports showed the relationship between HLA-DR alleles and cardiovascular mortality in other systemic/autoimmune diseases such as rhematoid artiritis and heart failure. This was concluded as a result of chronic inflammation (11-13). However, according to the best of our knowledge, there is no previous report which specifically investigated HLA Class II alleles in sarcoidosis according to the presence of DD. The aim of this study was to evaluate the frequency of left and right ventricular DD and its possible relationship between HLA DRB1* alleles in patients with sarcoidosis.

2. Materials and methods

2.1 Data Source and Study Design

The study was conducted in Cukurova University Faculty of Medicine Department of Chest Disease, which is a tertiary reference hospital in the region. The institutional ethics committee approved the study and written informed consents were obtained from all of the participants. Among 277 patients with sarcoidosis who had routine follow up in the unit since 2009, after excluding patients with known cardiac disease or who has abnormality in electrocardiogram, seventy-seven consecutive adult patients who had detailed echocardiography results and who were HLA-typed were included in the case control study. In 92.2% of patients, the certain diagnosis of sarcoidosis was confirmed with the existence of clinical symptoms, compatible radiology and biopsy that indicates noncaseating epitheloid cell granulomas, after exclusion of other known causes of granulomatosis as outlined by the joint statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS), and the World Association of Sarcoidosis and other Granulomatous Disorders (WASOG) (14). In the remaining 7.8%, biopsy was not obtained due to having Lofgren's syndrome defined as bilateral hilar lymphadenopathy, fever, ankle arthralgia and erythema nodosum. None of the patients complained any cardiac symptom or received steroid therapy at the time of diagnosis. Control group consisted of healthy volunteers with similar ethnicity, age and gender. None were relatives of the patient group.

After obtaining certain diagnosis, all patients underwent a standard evaluation routinely used and the following items were recorded: (i) A full medical history with physical examination, (ii) postero-anterior chest X-ray and computed tomography (CT) with high resolution images and hand radiography, (iii) lung function tests including carbon monoxide diffusion capacity (D_{LCO}), (iv) abdomen ultrasonog-

raphy, (v) ophthalmologic examination, (vii) tuberculin skin test and (vii) urinary calcium excretion in 24-hours. Chest X-rays were evaluated by an experienced chest physician specialized in diffuse lung disease, in terms of five "Scadding Stages" (Stage 0 to IV) in accordance with the ATS/ERS/WASOG Statement (14). Extra pulmonary organ involvement was defined according to ACCESS criteria (15). A resting electrocardiography (ECG) and echocardiography was performed to all patients at the time of diagnosis by the same investigator.

2.2 Pulmonary Function Tests

Pulmonary function tests (PFTs) were performed in the stable phase by using a calibrated Sensor Medics V Max 20 Spirometer according to the ERS guidelines (16). None of the patients were receiving oral or inhaled short-acting beta-2 agonists 8h before testing. Baseline forced expiratory volume (FEV_1) and forced vital capacity (FVC) was measured 3 times and the best of three measurements was recorded for the analysis. Total lung capacity was measured using the helium dilution technique (Jaeger MS-PFT Analyser Unit). The transfer factor of the lung for carbon monoxide(T_{LCO}) was measured using the single breath method. The results were presented as the percentages of predicted.

2.3 Typing HLA-DRB1 alleles

An isolation kit was used to extract DNA from venous blood sample of each subject (QIAamp DNA blood mini kit, cat no: 51104, QIAGEN Vertriebs GmbH, Vienna, Austria). Typing of HLA-DRB1 alleles from DNA samples were performed by Sequence Specific Oligonucletide Probes (SSOP) method. Tepnel Lifecodes HLA-DRB (Ref:628759-50, lot no: 10102Y, Connecticut, USA) typing kits were used for polymerase chain reaction (PCR) and hybridization procedures. This product consists of a combination of locus-specific oligonucleotide probes coupled to color-coded microspheres (Luminex Corp) and two PCR reactions. To type each sample, PCR was performed and the product was hybridized with the SSO-probe mixture using the manufacturer's protocol. After hybridization, the sample plate was located in a Luminex instrument for analysis.

2.4 Echocardiography

Transthoracic echocardiography was performed at the time of diagnosis to all study group according to current guidelines (The American Society of Echocardiography (ASE) and European Association of Echocardiography (EAE) guidelines) by a cardiologist using a 3 MHz sector probe with the generic Electric (GE) brand VIVID-S5 model 050684VS5N serial number device (17). Aorta, left atrium, interventricular septum (IVS), left ventricular end-systolic and end-diastolic diameters were measured using the M-mod method and ejection fraction (EF) was calculated by Teicholz method. Early (E) and late (A) diastolic mitral and tricuspid inflow velocities were measured by Pulsed wave Doppler (PWD) in apical 4-chamber view. Tissue doppler and PWD were used together to calculate S, A, E waves and ejection time (ET) over the lateral, septal and right ventricular free wall. Right ventricular dysfunction (RVDD) was defined as tricuspit valve E/A ratio <1 or >2. Left ventricular DD was defined as E/A ratio<1 or >2 on mitral valve with isovolumetric relaxation time (IVRT)> 90 milisecond (msn) or deceleration rate of early diastolic flow (Edec) >220 msn respectively.

2.5 Statistical Analysis

For the HLA analysis, tool that exist in web page of Los Alamos National Laboratory (http://www.hiv.lanl.gov/content/immunology/hla/) were used. For each HLA, the tool computes the 2-sided exact Fisher's p-value, which represents the probability that the observed difference is due to chance. In order to accurate the false discovery rate caused by the calculation of multiple p-values, Storey's q-value was also provided (18).

Continuous variables were compared with Student's t-test or with Mann Whitney-U tests. The chi-square test was used to compare the categorical variables. Variables were expressed as mean±standard deviation and n (%). Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) for windows release 20.0 (SPSS,Chicago,IL). Sample size calculation was performed with the predicted frequency of diastolic dysfunction in healthy population 1% and in sarcoidosis 10%. With the alpha value of 0.05 and 90% power, the required number was calculated as 77 for each

group. All *p* values were two-tailed, and a *p* of <0.05 was considered statistically significant.

3. Results

Seventy seven patients (51 female) with a mean age of 41.1 ± 8.2 years (yrs) at the time of diagnosis and seventy seven healthy controls with a similar age (38.7 ± 7.8 yrs) and gender (female/male: 51/26) were included in the study. The majority were never smokers (69.8%) and the duration of symptoms was 4.6 ± 5.4 months. There were 32 patients at Stage I, 39 patients at Stage II and 6 patients at Stage III at the time of diagnosis. There were no patients at Stage IV. Twenty nine patients (37.7%) received systemic treatment while 48 (62.3%) of them did not received any systemic treatment. Extra-pulmonary involvement were present in 32 patients (41.6%). The most common extra-pulmonary involvement was skin (n=16) followed by Lofgren syndrome (n=12). Patient characteristics were summarized at Table 1.

Electrocardiography results of the patients were normal in terms of PR and QT interval and heart block or arrhythmia was observed in none of the patient group. According to standard definitions, the frequencies of LVDD and RVDD were remarkably higher in sarcoidosis patients than the controls (26% vs. 2.6% for LVDD and 42.9% vs. 18.2% for RVDD, respectively) (p<0.05). When the sarcoidosis patients compared with the control group, the age and gender was similar however Mitral A wave, tricuspit E wave, tricuspit A wave, right ventricular diameter and Edec values were higher; while mitral E/A ratio and tricuspit E/A ratio were significantly lower in patients with sarcoidosis (Table 2) (p<0.05).

The evaluation of the sarcoidosis group according to the presence of either LVDD or RVDD revealed nonsignificant results in terms of age, gender, smoking history, body mass index, the presence of extrapulmonary involvement and respiratory function tests (Table 3).

The distribution of the HLA-DR alleles according to the presence of diastolic dysfunction in patients with sarcoidosis were shown in Figure 1. Twelve different HLA-DR alleles including HLA-DRB1*04, HLA-DRB1*15, HLA-DRB1*03, HLA-DRB1*16, HLA-DRB1*12, HLA-DRB1*14, HLA-DRB1*13, HLA-DRB1*07, HLA-DRB1*11, HLA-DRB1*01, HLA-DRB1*08 and HLA-DRB1*10 were documented in patients with sarcoidosis. The distribution of HLA DRB1* alleles were alike among patients with or without RVDD (p>0.05) (Figure 1a & Supp. Table 1). For the LVDD, HLA DRB1*14 allele was

Table 1. Characteristics of the patient group

Characteristics	Number (%)
Number of patients	77
Females	51 (66.2)
Males	26 (33.8)
Mean age at disease onset (years ± SD)	41.1 ± 8.2
Smoking history	
Never smokers, n (%)	53 (69.8)
Smokers, n (%)	24 (31.2)
Grade of disease at the time of diagnosis (n)(%)	
1	32 (41.6)
2	39 (50.6)
3	6 (7.8)
4	0 (0)
Respiratory function tests (mean ± SD)	
• FEV_1/FVC	79.0 ± 8.5
• FEV_1 (%)	83.3 ± 16.4
• FVC (%)	85.5 ± 10.8
• DLCO (mmol/min/kPa)	78.8 ± 16.8
Biopsy confirmation, n (%)	71 (92.2)
Lofgren's Syndrome, n (%)	6 (7.8)
Positive extra-pulmonary involvement, n (%)	32 (41.6)

Table 2. Comparison of the patient and control groups in terms of echocardiographic findings indicating diastolic dysfunction

	Sarcoidosis Group (n=77)	Control group (n=77)	p
Age (years)	41.1 ± 8.2	38.7 **±** 7.8	0.060
Female Sex (n) (%)	51 (66.2)	51 (66.2)	1
Mitral E wave (cm/s)	71.4 ± 18.8	73.7 ± 15.6	0.403
Mitral A wave (cm/s)	63.3 ± 15.8	55.1 ± 14.6	**0.001**
Mitral E/A ratio	1.19 ± 0.38	1.39 ± 0.33	**0.001**
IVRT	92.2 ± 17.0	91.9 ± 22.2	0.916
E dec (msn)	205.4 ± 48.8	191 ± 32.8	**0.034**
LVDD frequency, n (%)	20 (26)	2 (2.6)	**0.000**
Tricuspit E wave (cm/s)	18.6 ± 5.4	12.3 ± 2.2	**0.0001**
Tricuspit A wave (cm/s)	20.2 ± 8.5	9.9 ± 3.3	**0.0001**
Tricuspit E/A ratio	1.03 ± 0.38	1.34 ± 0.36	**0.0001**
Right Ventricular diameter	26.4 ± 3.6	24.6 ± 2.9	**0.001**
RVDD frequency, n (%)	33 (42.9)	14 (18.2)	**0.001**

E dec: Deceleration rate of early diastolic flow, LVDD: left ventricular diastolic dysfunction, RVDD: right ventricular diastolic dysfunction

Table 3. Comparison of the patient group according to the presence of diastolic dysfunction

	LV Diastolic Dysfunction (+) (n=20)	(-) (n=57)	p	RV Diastolic Dysfunction (+) (n=33)	(-) (n=44)	p
Females, n (%)	11(55.0)	40 (70.2)	NS	21 (63.6)	30 (68.2)	NS
Age (years)	42.8 ± 8.2	40.5 ±8.2	NS	42.7 ± 7.9	40.0 ± 8.3	NS
BMI	30.8 ± 5.2	29.6 ± 4.9	NS	30.5 ± 3.9	29.5 ± 5.6	NS
Smokers,n (%)	9 (45.0)	15 (26.8)	NS	10 (30.3)	14 (32.6)	NS
FEV_1/FVC	78.1 ±7.2	79.3 ± 9.0	NS	77.3 ± 7.8	80.3 ± 8.9	NS
FEV_1 (%)	82.5 ±12.8	83.6 ± 17.6	NS	82.7 ± 15.4	83.8 ± 17.3	NS
FVC (%)	86.5 ± 9.4	85.2 ± 11.3	NS	86.6 ± 9.3	84.7 ± 11.9	NS
DLCO	80.6 ± 20.1	78.2 ± 15.6	NS	79.6 ± 18.2	78.2 ± 15.8	NS
EPI,n (%)	9 (45.0)	23 (40.4)	NS	13 (39.4)	19 (43.2)	NS

BMI: Body mass index, EPI: Extrapulmonary involvement

more common in patients with DD according to p value however; the statistical significance was lost in the further p-corrected (q-value) analysis (Figure 1b & Supp. Table 1).

4. Discussion

The present study indicates that the frequency of biventricular DD is remarkably high in patients with sarcoidosis. To the best of our knowledge, our data is the largest cohort, which specifically investigates the frequency of DD in sarcoidosis. In addition, for the first time we have investigated the genetic basis of DD and have showed that HLA DRB1*14 allele may be related with LVDD in sarcoidosis.

The diagnosis of cardiac involvement in sarcoidosis is a real clinical dilemma. The clinical diagnostic criteriae state only probable disease (19-21). In addition, the conventional diagnostic tools including ECG, Holter monitoring, echocardiography, radionuclide studies and the new technology methods such as cardiac magnetic resonance imaging and positron emission tomography (PET) have been accepted to be unsatisfactory (8,21). Quantitative interpretation of PET scan have been suggested to reduce interventions in cardiac sarcoidosis (22). In another recent report, adding a pathologic ECG to an elevated NT-pro-BNP predicted cardiac involvement with a specificity 93% and sensitivity 78% (23). Although the histological diagnosis performed by endomyocardial biopsy is considered the gold stand-

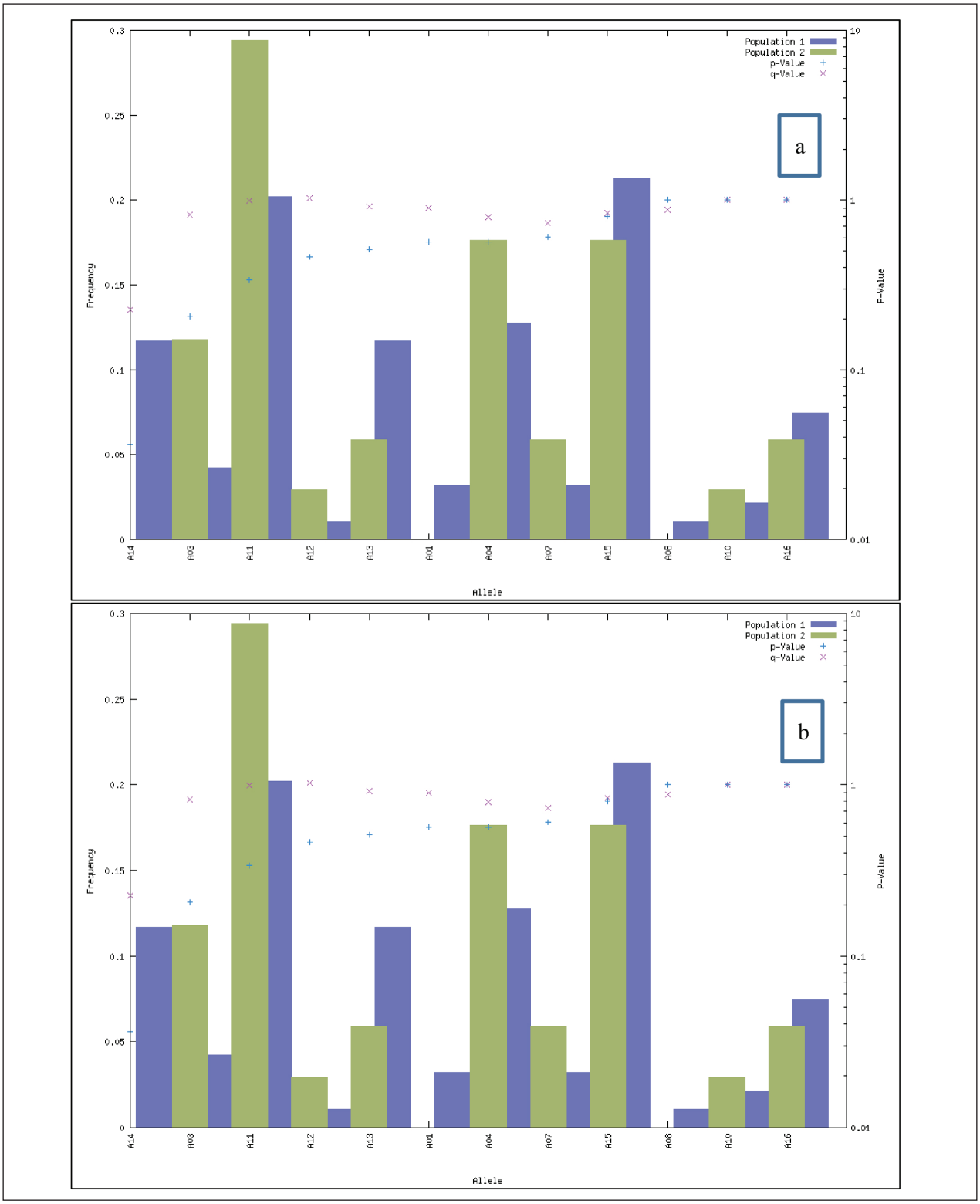

Fig. 1. The frequency of HLA Class II alleles according to the presence of (**a**) RVDD and; (**b**) LVDD. Blue bars represent positivity of diastolic dysfunction in both figures. Although there were comparability between groups especially in HLA DRB1*14 allele in patients with DD according to p value, presence of alleles did not show significant differences after correction (q) analyses

ard method with high specificity, it has low sensitivity (20-30%) due to the focal involvement nature of the disease (24). Consistent with the recent reports, most of the patients seems to be underdiagnosed.

DD is not a well-defined form of sarcoidosis. Major general risk factors of DD include age, hypertension, diabetes mellitus and left ventricular hypertrophy (25). According to an epidemiological study, asymptomatic mild LVDD is reported in 21%, and moderate to severe DD is present in 7% of the population (26). In another population based cohort study, the frequency of DD was 41% among elderly women (27). In an epidemiological study performed in Turkish population, the prevalence of DD was 67.6% (28). Current literature shows a latent phase between the development of DD and heart failure however especially moderate-severe DD have been associated with an increased risk of heart failure and those related mortality (25).

Sarcoidosis has not been a well-defined risk factor of DD, therefore the current literature on DD and sarcoidosis is extremely limited. In a previous cross-sectional study, fifty consecutive subjects who had biopsy specimen-proved pulmonary sarcoidosis without suspected cardiac involvement were compared with 30 healthy controls in terms of LVDD. As a result, DD was found to be present in 14% of the patients which was approximate with the control group. Those with DD had a longer duration of illness and were significantly older than the controls ($p<0.05$) (9). In a retrospective cohort study, RV contractile dysfunction was common (46.5%) in patients with sarcoidosis without manifest cardiac involvement or pulmonary hypertension (29). Another study performed in our country which evaluated 28 patients and 24 healthy subjects indicated that RV diastolic parameters were significantly lower in patients with sarcoidosis (30). Patel et al. confirmed these results with a very high rate of RV dysfunction (56%)(31). LV function was found to be significantly impaired in sarcoidosis patients as compared with control subjects, despite the absence of clinical or standard echocardiographic evidence of cardiac involvement. The authors concluded this result probably as the presence of subclinical myocardial dysfunction (32). In our study, the frequency of both LVDD (26%) and RVDD (42.9%) were significantly higher than the controls. In addition, the frequency of DD in sarcoidosis patients were comparable with the previous reports (29). There were no significant difference between patients with or without DD in terms of demographical, clinical and physiological features.

The potential effect of HLA-DR alleles on DD is still a mystery. A previous report performed on rheumatoid artritis patients indicated that HLA DRB1* alleles were linked with cardiovascular mortality independent from the presence of traditional atherosclerosis risk factors (11). A meta analysis addressed an association between HLA DR alleles and risk for rheumatic heart disease with a significant heterogeneity among different ethnic and racial groups (12). Another meta analysis which included 1,378 cases and 10,383 controls from 19 studies reported certain HLA-DR alleles as a potential risk factor of idiopathic dilated cardiomyopathy (13). To date, a wide range of HLA-DR alleles have been accused for sarcoidosis pathogenesis however the genetics of cardiac sarcoidosis is complex in terms of contributing to the susceptibility and severity of heart involvement (33). HLA-DQ alleles were previously associated with the susceptibility to cardiac sarcoidosis (34). In this study, for the first time we have reported that HLA DRB1*14 allele may be a potential risk factor of LVDD. From a biological point of view, this result is plausible. Previous molecular studies showed that different HLA DRB1* alleles present different Th1 responses which present a different peptide profile and promote an aberrant Th1 immunity. This response leads to increased IFN-γ, TNF-α and decreased TGF-β levels and results in not only ineffective clearance of the pathogenic antigen(s), but also a continual release of profibrotic cytokines (35). Thus, chronic inflammation may lead to DD in sarcoidosis.

The possible mechanism of DD which is characterized by impaired LV relaxation with increased LV stiffness is not well defined. Patel *et al* reported that RV dysfunction is usually associated with either direct LV involvement, lung disease, or pulmonary hypertension, but may occur in the absence of these mechanisms, suggesting the possibility of isolated RV involvement (31). Many other mechanisms have also been proposed including cardiac oxidative stres, alterations in intracellular Ca^{2+} transients, titin isoform shifts, fibrosis and posttranslational modification of cardiac myosin binding protein C (25). These mechanism of DD may also be the underlying reason of DD in sarcoidosis however there may also be

other pathways to explain the possible link. Since no report specifically investigated the potential mechanism of action, further studies on the pathogenesis of DD in sarcoidosis are required.

Several limitations of this study should also be taken into account. First of all, we could not confirm our results by another imaging modality such as MRI, PET-CT or radionuclide scintigraphy in all of the patients. Second, no long term follow up was performed since it was a case control study. Third, our sample size was calculated according to the prediction of DD, without including HLA analysis, in the study group. Although we showed the impaired biventricular DD in the largest cohort to date, our results still reflect a small sample size of a single ethnic group. The potential role of DD and its relationship with HLA DRB1* alleles needs to be investigated in further larger cohorts in different ethnic groups.

In conclusion, this study showed that biventricular DD is a common entity in patients with sarcoidosis. HLA DRB1*14 allele may be related with LVDD in these patients. Because of the reason that echocardiography is a recommended initial screening test, right and left ventricular DD parameters should be measured in all patients with sarcoidosis. DD may be a significant clue in clinically silent cardiac involvement of sarcoidosis. Long term follow up results of these patients may clarify the right approach and affect the prognosis in these patients. In addition, the potential mechanism of DD and the possible link between HLA DRB1* alleles in sarcoidosis warrants further investigation.

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