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THE IMPACT OF HUMAN LEUCOCYTE ANTIGEN CLASS II DRB1*/DQB1* ALLELES IN SARCOIDOSIS OCCURRING IN ETHNIC INDIANS

Pulmonary Medicine

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ABSTRACT

Sarcoidosis in India differs in many aspects from that of other ethnic groups. In order to assess the phenotypes related to alleles and also to make prognostication, an evaluation of Class II HLA alleles DRB1 and DQB1 was done in cases of Sarcoidosis at various stages of presentation and progression. **Materials and methods:** Fifty cases of sarcoidosis of Indian origin who were followed up for at least three years in remission or five years in non remission or until death during the study were taken up for assessment. There were 25 females and 25 males. Phenotypic grouping was done as Stage I and a second group of all those in Stage II-IV. Included in this group also was Stage 0. **Results:** It was found that HLA-DRB1*14, and HLA-DRB1*07 were poor prognosis genes as in other studies. However in variance from other groups HLA-DRB1*15 was found to be associated with a good prognosis. HLA-DRB1*11 gave a variable result. HLA-DQB1*02 and HLA-DQB1*06 were associated with uveitis in Stage-I, unlike the studies from Japanese and Dutch patients, where HLA-DRB1*04 was commonly seen in uveitis. The allele associated with Lofgrens syndrome (LS) in Sweden, HLA-DRB1*03 was rarely seen, and LS not seen in its full form. **Conclusion:** Genetic evaluation of Sarcoid patients using Class II HLA- DRB1* and HLA-DQB1* alleles can help in prognosticating and identifying patients who need prolonged follow up even if in remission. Also it may predict relapse and identify those in whom a close follow up is required as they are at risk of long term effects of the disease.

KEYWORDS

INTRODUCTION

Sarcoidoisis is an enigmatic disease, having several confounding factors. After years of intense research a unifying theory remains elusive. There is no doubt that it is initiated by exposure to an antigen that stimulates granuloma formation in various tissues.(1) Thereafter the disease may remit or progress due to as yet unknown reasons. Ethnicity, familial factors, environment all appear play a role in the world wide phenotypic variations.(2)

The existence of Sarcoidosis in India is a relatively recent discovery. The overwhelming preponderance of tuberculosis which it resembles has always overshadowed Sarcoidosis in this region.(3) It has been seen that Sarcoidosis in Indians is relatively benign as compared to Africans. Lofgrens syndrome (LS), Heerfordt syndrome (HS) are rarely seen with the complete manifestations. We have also found hypercalcemia to occur with much less frequency. However Uveitis, skin involvement (without erythema nodosum), and arthritis are commonly associated with bilateral hilar lymphadenopathy (BHL) in the early stage disease.(4) We have also noted a unique manifestation where proved Mycobacterium tuberculosis positive disease turns into Sarcoidosis which has been termed Tuberculo-sarcoid.(5).

For purposes of study, the disease can be grouped into an early stage of which bilateral hilar lymphadenopathy (BHL) is a part. Extra pulmonary manifestations (EPM) may or may not be present. These may occur as the complete Lofgren's syndrome (LS) or have partial manifestations. At this stage the disease tends to remit more commonly than progress. A second group is the later stage disease with pulmonary parenchymal and mediastinal lymphnode or purely parenchymal involvement where the disease remission becomes less common. A third group comprises of patients with only purely extra pulmonary manifestation, here disease tends to be non-remitting.(6)

Research in various countries has shown that HLA Class II antigens determined by HLA- DRB1/DQB1 alleles play a role in Sarcoidosis and its varied presentations. For instance in Sweden where a large proportion of patients with LS are found, the HLA- DRB1*03 allele has been linked to it, albeit with a favourable prognosis. In the same ethnic stock it has been seen that HLA- DRB1*04 and HLA-DRB1*15 alleles are associated with non –LS presentations along with extra-pulmonary manifestations (EPM). Those with non-remitting disease commonly have at-least one of HLA- DRB1*07/*14/*15 alleles.(7) A similar association for non-remitters (NR) was found in patients studied in Turkey.(8) On the other hand LS is rarely seen in Japan, where Uveitis is a more common presentation. Here the HLA-DRB1*04 allele is found to be associated with this presentation. Interestingly the HLA- DRB1*03 allele is very rare in Japan.(9)

HLA-DRB1/DQB1 alleles are central in the role of determining some of the receptor proteins of the antigen presenting cells and affect T cell interactions that initiate granuloma formation.(10) The result of studies on this subject are summarized in Table-1.

TABLE 1

DISTRIBUTION OF HLA CLASS II ALLELES IN VARIOUS COUNTRIES

Sr No	Allele	Prognosis	Region/ Country
1	DRB1*14	NR/Non LS	(13), (19), (8) Turkey; (7) Sweden; (9) Japan; (9) UK; (11) India
2	DRB1*07	NR	(8) Turkey; Protective (11) India
3	DRB1*15	NR	(8) (19) Turkey; (7) Sweden; (17) US; (23) Finland
4	DRB1*11	NR/Non LS Decreased EPM	(19) Turkey; Increased Sarcoid risk(17) US; R (11) India
5	DRB1*13	NR/Non LS Decreased EPM	(12) Turkey
6	DRB1*10	R	(12) Turkey
7	DRB1*04	Increased EPM Uveitis	(17) US; (14) (15) Sweden; (9) Japan; HS(14) Sweden
8	DRB1*03	R(LS)	(7), (20) (9) Sweden; (9) Dutch; Absent(9) Japan
9	DRB1*01	R	(7) Sweden; (9) Japan
10	DRB1*12	NR	(9) Sweden; (22) US
11	DQB1*06	NR	(12) Turkey
12	DQB1*05	Protective	Protective (9) Japan; (11) India
13	DQB1*06/DRB1*15	NR	Severe(16) Netherland
14	DQB1*02/DRB1*03	Protective	Protective (16) Netherland; (11) India
15	DRB1*15/03	R	(7) Sweden
16	DRB1*14/15	NR/EPM	(14) Sweden
17	DRB1*07/DQB1*02	Protective + decreased Severity	(9) Sweden
18	DRB1*04/DQB1*03	R Uveitis	(9) Japan; UK

R remitter, NR Non remitter, LS Lofgrens Syndrome, EPM extra pulmonary manifestations, HS Heerdfordt Syndrome,

There has been only one prior study evaluating HLA- DRB1/DQB1 alleles in this region.(11) We have studied class II HLA-DRB1 and HLA- DQB1 alleles in patients with Sarcoidosis in India, to see if they are a) present in similar manner to the alleles in other countries and continents b) if they define phenotypes in the same way c) if they are protective or increase severity by their presence, as has been noted in other ethnic groups.

MATERIALS AND METHODS

This study includes all proved cases of Sarcoidosis who presented to the first author in Indraprastha Apollo hospitals, New Delhi between the years 2010 to 2015. All patients were of Indian ethnic origin and

followed up for a minimum of three years after remission or uptil at least 5years, or more till termination of the study in 2020 in non-remitters, or uptil death during the course of the study. Those who did not meet this time line criteria were excluded from the study.

The diagnosis of Sarcoidosis being one of exclusion, each person was extensively evaluated clinically including eye and skin examination. The patients were also investigated with haematological, biochemical profile, ECG, 2D ECHO, PFT including diffusion study and 6minute walk test (where indicated), Mantoux test, CECT Thorax and Ultrasonography of abdomen. Biopsy of involved sites were done including cervical, axillary lymphnode biopsy, as well as of liver and skin. Bronchoscopy with FNAC from mediastinal gland using EBUS and TBLB was performed where indicated.

The patients were classified into radiological Stage 0 having only extra pulmonary involvement, Stage 1 patients with BHL but no pulmonary parenchymal involvement, Stage II patients with BHL or mediastinal lymphnode enlargement and pulmonary parenchymal infiltrates, Stage III and IV no significant mediastinal lymphnode involvement but parenchymal infiltrates with (Stage III) or fibrosis (Stage IV).

A cohort of controls comprising normal transplant donors of Indian ethnicity were incorporated into the study for assessing allele frequency in the general population and comparison with the study group.

The outcomes of the disease were defined as prolonged remission (R) where no drug therapy was required for at least as long as follow up (Minimum 3 years), and non-remitters (NR) who either had progressive disease, or multiple relapses requiring drug therapy for control.

HLA CLASS II DR ALLELES TYPING

This was done after taking informed consent of the patient. They were made aware that the test would be used for research purposes to help Sarcoidosis patients in general and if possible in their case also, but it may not necessarily be so.

DNA was extracted from peripheral leukocytes by DNA isolation kit (Invitrogen USA PURELINKTM Genomic DNA minikit) and DNA stored according to manufacturer's instructions at -20 degrees Celsius till further analysis.

Low resolution HLA typing for HLA-DR and DQ loci was performed by PCR sequence specific primer (PCR –SSP) method (All Set TM Gold SSP HLA-ABDR, life technologies, USA) with DNA of 50ng/ul concentration utilizing allele specific primers along with control primers to identify the respective allele for HLA DRB1 and HLA DQB1. Amplified products were run on 2% agarose gel and gel image captured in gel documentation system and interpreted by Unimatch 6.0 CE-IVD software (Life Technologies Corporation).

STATISTICAL ANALYSIS

Statistical analysis was performed using SSPS Statistical software version 22.0 and R.3.2.0. Categorical variables were expressed as count and percentages. Z-Test of proportion and Odd Ratio were calculated to compare proportions of Alleles in disease development between case and control. P–value of less than 0.05 was considered to indicate statistical significance.

RESULTS

A total of 50 patients were taken up for study. There were also 100 controls. There were 25 males and 25 females each in the study. At the time of incorporation into the study there was only one patient above 70years of age and four below thirty. The rest of the 45 patients were between 30 and 70years of age.

There were 15 patients in Stage I, 24 patients in stage II, 9 patients in stage III and IV together and 2 patients in stage 0 with pure EPM disease. In the stage I disease 13 patients went into prolonged remission, one patient died after 5 years of follow up with cardiac sarcoidosis, and disease persisted in one patient. In Stage II disease 10 patients went into prolonged remission, whereas in 14, drug treatment was required to control the disease (non remitters). In the patients with stage III/IV disease there were 7 non remitters, 0ne death occurred after 8years follow up due to advanced ILD, and one patient went into prolonged remission. Both the patients in Stage 0 with pure EPM were non remitters.

Uvietis with or without EPM was seen in 7 patients of stage I disease. EPM without uveitis were seen in 4 patients in Stage I, 5 patients of Stage II, and both the patients of stage 0.

One patient had Tuberculo-sarcoid as defined earlier, and there was one familial cluster of two brothers.

The frequencies of occurrence of HLA-DRB1* are given in Table-2 for all cases grouped in Stage 1 followed by a grouping for all other stages. The frequencies of HLA DQB1* are similarly grouped in Table-3.

TABLE 2

RESULTS OF CLASS II HLA ALLELES DRB1 TYPING ALONG WITH CONTROLS

STAGE I					
SR NO	ALLELES	PATIENTS n= 15/Alleles(30)	CONTROL n= 100(Alleles 200)	P	OR
1	DRB1*15	36%	18%	0.018	2.64
2	DRB1*07	23%	13%	0.131	2.04
3	DRB1*03	10%	12%	0.81	0.81
4	DRB1*14	10%	6%	0.406	1.74
5	OTHERS	21%	51%		
STAGE II, III, IV,0					
SR NO	ALLELES	PATIENTS n= 35/Alleles(70)	CONTROL n= 100(Alleles 200)		
1	DRB1*14	30%	6%	0.001	6.71
2	DRB1*15	21%	18%	0.528	1.24
3	DRB1*11	11%	10%	0.727	1.16
4	DRB1*07	10%	13%	0.509	0.74
5	DRB1*03	7%	12%	0.258	0.56
6	OTHERS	21%	41%		

The frequency of occurrence of HLA-DRB1 alleles in Stage 1 was seen to be significantly ($p<.05$) increased for HLA-DRB1*15 with an odds ratio (OR) of 2.64. (Table-2). The frequencies of other alleles was not significantly (NS) increased for other alleles. But the OR was increased for HLA- DRB1*07 (OR- 2.04) and HLA-DRB1*14 (OR-1.74) alleles. In the grouping of all other stages for HLA-DRB1* it was seen that HLA-DRB1*14 allele was significantly ($p< .05$) increased with an OR of 6.71. All other frequencies were not significantly different from controls, although the OR of HLA-DRB1*15 was 1.24 and OR of HLA- DRB1*11 was 1.16.

Considering the frequencies of HLA- DQB1* in Stage I (Table-3), only HLA-DQB1*02 allele was found to be significantly (<.05) increased from controls, with OR of 2.44. Other alleles with OR more than 1.0 were HLA-DQB1*05 with OR 1.39 and HLA- DQB1*06 (OR 1.03). In all other stages only the DQB1*05 allele was significantly ($p<.05$) increased with an OR ratio of 2.38.

To further understand the effects of alleles on phenotypes, homozygous states at either DRB1 or DQB1 were considered because this would eliminate effects of other alleles.

HLA-DRB1*15 homozygous (HZ) state was seen in 3 patients all went into prolonged remission, one such patient was associated with HLA-DQB1*05 HZ state and another with HLA-DQB1*06 HZ state. HLA-DQB1*06 HZ state was also seen in another case with HLA-DRB1*14/15, but this case was a NR.

HLA-DRB1*07 HZ state seen in one patient who died with cardiac sarcoidosis associated with homozygous state DQB1*03/03 HLA-DRB1*04 HZ state was seen in one patient whose disease remitted.

HLA-DRB1*14 HZ state was seen in 5 patients all 5 were non remitters. One such patient had tuberculo-sarcoid (associated with HLA-DQB1*05/06). Three patients were haplo-identical HZ associated with DQB1*05/05. One of these also had CNS sarcoidosis.

HLA-DQB1*02 HZ state was seen in one patient who died due to advances ILD. It was associated with HLA-DRB1*03/07 HLA-DQB1*06 HZ state was seen in two patients as mentioned above.

HLA-DQB1*03 HZ state was seen in one patient along with HLA-DRB1*09/11 who had prolonged remission.

Non-homozygous but haplo-identical patients were grouped together, looking at phenotypes across stages.

HLA-DQB1*05/06-DRB1*14/15 haplotype was seen in four patients. There was one patient in Stage 1 who went into remission.

There were two patients in Stage II. One patient went into in remission and one was NR.

There was one patient in Stage IV with progressive disease.

There were two more patients haplo-identical at only HLA-DRB1*14/15 with progressive disease HLA-DQB1*02/05-DRB1*03/14 haplo-identity was seen in three patients.

There was one patient in Stage 1 who went into remission
There were two patients in later stages both were NR.

HLA-DQB1*03/05-DRB1*05/07 non homozygous haplo-identical state was found in two brothers, both in stage II and both NR.

HLA-DQB1*03/05-DRB1*11/14 haplo-identity was seen in three patients

There was one patient in Stage 0 who was NR.
There were two patients in Stage II one in remission, one NR
HLA-DQB1*02/06-DRB1*07/15 haplo-identity was seen in two patients Both patients were in Stage 1 and went into remission, one presented with uveitis. Haplo-identical state at only HLA-DRB1*11/15 was seen in two patients.

Both patients were in Stage II-IV and both were NR
Haplo-identical state at only HLA-DRB1*13/15 was seen in two patients Both had remitting disease in Stage 1.
Haplo-identical state at only HLA-DQB1*02/06, was seen in two patients both went into remission and both had uveitis.
Haplo-identical state at only HLA-DQB1*05/06 was seen in three patients One case was in Stage 1 and NR, associated wiith EPM including Uveitis. Two cases were in Stage II both NR with EPM.

There were seven cases of EPM with uveitis in Stage 1 and they had either HLA-DQB1*02/06 allele (three patients), HLA-DQB1*02 (three patients) or DQB1*06 (one patient). However there were other patients in the HZ state in other stages of HLA-DQB1*02 or HLA-DQB1*06 as mentioned above who did not have uveitis.

DISCUSSION

The assumption of genetic association with Sarcoidosis has been easy to presume, but difficult to prove, especially as there are a lot of ethnic and loco-regional variations in severity, phenotypes, as well as allele associations. For instance the LS phenotype so readily found in Sweden and having a good prognosis is linked with allele HLA-DRB1*3. But this is not seen in Japan at all where uveitis predominates associated with HLA-DRB1*04.(9) In any population it will have to be presumed that these alleles are linked in disequilibrium with other as yet unspecified loci that also play a significant role.

In our study in Stage 1 the frequency of HLA-DRB1*15 was found to be twice that of the controls ($p<.05$). HLA-DRB1*07 was also seen to be present in a frequency greater than controls but not significantly so. It is to be noted that HLA-DRB1*03 was lower than in controls and DRB1*14 was a little higher than controls however their frequency was not significantly different from controls.(Table-2)

On analyzing the HLA-DRB1*15 homozygous state seen in three patients, it was seen that all three patients went into prolonged remission. Thus in the Indian population the presence of this allele gives a good prognosis. This is at variance with the findings of studies done in Turkey and Sweden where this allele was associated with a poor prognosis.(7,8,19).

There was one patient homozygous for HLA- DRB1*07 who died of cardiac sarcoidosis, another HLA-DRB1*07 homozygous patient in stage II was a non remitter and significantly there was one patient in stage IV with a single allele of HLA-DRB1*07 who died of advanced interstitial lung disease. There were two brothers who were haplo-identical in Stage II, both had HLA-DRB1*07 allele and both required drug treatment to maintain remission. It is thus inferred that the presence of this allele worsened the prognosis of the patient. This allele was seen to be associated with a NR state in Turkey (8).

There were two patients with haplo-identical HLA-DRB1*07/15 in stage I , both had remitting disease, thus showing the presence of HLA-DRB1*15 dominated over the poor prognosis allele HLA-DRB1*07.

Looking at the HLA- DQB1* alleles in Stage 1 it was found that HLA-DQB1*02 was almost twice in frequency of controls ($p<.05$) and HLA-DQB1*03 was almost half the frequency of controls. Homozygous states were seen in HLA-DRQB1*02 who died of advanced ILD as mentioned above associated with DRB1*03/07 alleles. HLA-DQB1*06 HZ state was seen in a patient who was a non-remitter and in another who was a remitter. Thus here the influence of HLA-DRB1* probably play a more significant role. On the other hand HLA-DQBI*03 HZ state was seen in one patient whose disease went into prolonged remission. Hence this allele was associated with a good prognosis.

It was seen that HLA-DQB1*02 (3 cases) and HLA-DQB1*06 (1 case) alone or together as HLA- DQB1*02/06 (3 Cases) were associated with uveitis in Stage1. All these cases went into remission. DQB1*02 has been an allele associated with good prognosis in UK and Netherlands(26).

In Stages II,III, IV and 0 it was found that the most common DRB1 allele was HLA- DRB1*14 having a frequency double that of controls ($p<.05$). In the homozygous state seen in 5 patients with HLA-DRB1*14 it was noted that all were non remitters. These included three patients with haplo-identical DQB1*05/05-DRB1*14/14, of these one patient had CNS sarcoidosis. DQB1*05 has been noted to be protective but this was not confirmed in our study(9,11). In fact in the later stage disease HLA-DQB1*05 was seen to be the most commonly occurring allele ($p<.05$) however it seemed to be neutral, and not modifying the disease when associated with good or bad prognosis alleles. HLA-DRB1*14 allele has been associated with a poor prognosis in other countries also, viz Turkey, Sweden, Japan, Uk, and India.(7,8,9,11,13, 19)

There were four patients heterozygous but haplo-identical at HLA-DQB1*05/06-DRB1*14/15. Two of these patients were in remission, while two had progressive disease. Two more patients haploid-identical at only HLA-DRB1*14/15 had progressive disease. Thus when HLA-DRB1*14 was present with HLA-DRB1*15 the prognosis was variable but tending towards progressive disease.

Another trio of patients were heterozygous but haplo-identical at HLA-DQB1*03/05-DRB1*11/14 where two were non- remitters and one was in remission. It was again seen that the presence of HLA-DRB1*14 allele worsened the prognosis. It is possible that a patient may have a prolonged remission and recurrence may later with a poor prognosis allele but this could not be proved in our study.

The presence of HLA-DRB1*13/15 was seen in two cases, both of whom went into remission. However in four cases of haplo-identity at HLA-DRB1*11/15 two cases remitted and two were non remitters.

The haplo-identical state of HLA-DRB1*03/14 was present in three cases two of whom were non remitters and one remitter.

From the above it can seen that in Indian patients, the alleles which could be attributed to remitting disease and non-remitting disease were somewhat different from other continents and ethnic groups.

In our study, the presence of HLA-DRB1*15 assured of a remitting disease especially in the homozygous state. But in Turkey, Japan and Sweden it was associated with poor prognosis.(7,8,9)

When both the alleles HLA-DRB1*14/15 were present together, the outcome was variable but tending towards non remission. This was in conformity with Swedish studies(14)

Another allele HLA-DRB1*07 also was indicative of progressive disease singly or in homozygous state except when present with DRB1*15, where it was associated with remitting disease. In the Netherlands this allele was associated with HS(14) and non-remission except when associated with HLA-DQB1*02 when its prognosis shifted to remitter.(9) The latter was not seen in our study, in fact one patient was homozygous for HLA- DQB1*02 and associated with HLA- DRB1*07 had progressive disease and died from it.

Unlike in Sweden where HLA-DRB1*03 was frequently present and associated with LS, we did not see any classic case of LS. In fact the

frequency of this allele was less than controls in stage I disease. However its presence was favourable, although no patient in the homozygous state was seen to evaluate its full effect. When associated with HLA-DRB1*14, it improved the prognosis in one patient but not in two others. Similarly the allele HLA-DRB1*04 which is so commonly associated with uveitis in Japan was rarely seen in our patients although its presence in one patient with homozygous state, was associated with remission, but there was no case of uveitis associated with it.

In our patients we found the alleles HLA-DQB1*02 and HLA-DQB1*06 to be associated with uveitis and remitting disease in Stage I. HLA- DQB1*02 was also associated with uveitis and good prognosis in Dutch patients.(16). This was in contrast to Japan and UK where Uveitis was associated with HLA-DRB1*04. (9,14,17). However in later stage disease the HLA-DRB1* alleles appeared to dominate the outcome over HLA-DQB1* alleles.

As an example HLA-DQB1*06 was seen as a non-remitter allele in Netherlands and increased the severity of HLA-DRB1*15. (16) This was not seen in our study, where even in a homozygous state HLA- DQB1*06 did not worsen the good prognosis of HLA-DRB1*15/15 in one patient.

Another allele HLA-DRB1*11 seemed to be linked to a variable response, improving the prognosis when associated with HLA-DRB1*14 and worsening it, when associated with HLA-DRB1*15. In the USA HLA-DRB1*1101 was associated with a higher risk of Sarcoidosis in whites as well as African-Americans(17). This allele was also associated with Non LS disease in Turkey, and commonly found in the previous Indian study (11,19). Another allele, HLA-DRB1*13 was seen in Turkey to be associated with Non LS state (12). This allele was seen to be favourably associated with HLA-DRB1*15 in our study, where two patients went into prolonged remission.

To conclude we have linked disease phenotypes of Sarcoidosis with the presence haplo-identical homozygous or heterozygous alleles. Although the numbers are small we have been able to see how their presence modifies the disease state. We have thus found that in Indian patients, HLA-DRB1*14 and HLA-DRB1*07 alleles were associated with a poor prognosis whereas HLA-DRB1*15 was associated with a good prognosis. Further the presence of HLA-DRB1*15 with HLA-DRB1*07 improves the prognosis of HLA-DRB1*07.

We also found that HLA-DQB1*02 and HLA-DQB1*06 were associated with Uveitis in Stage 1. We did not find HLA-DRB1*03 to be present in significant numbers, also we had no cases of the full blown LS or HS. Lastly when HLA-DRB1*14/15 were present together the disease tended to progress, and with HLA-DRB1*11/14 or HLA-DRB1*11/15 the outcome was variable.

The findings of this study can be used to predict the prognosis of the patients presenting with Sarcoidosis. An evaluation of HLA –Class II alleles of DQB1 and DRB1 would also indicate that those patients with 'bad prognosis ' alleles should be kept under observation even if they go into remission as they may later develop more advanced disease.

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