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Original Article

Hla-B27 Allele Connotation Amongst Individuals Conjectured of Spondyloarthritis (SPA) In Pakistan

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ABSTRACT

Objective: To define the link of HLA-B27 with Spondyloarthritis (SPA) among the study population.
Study Design: Cross-sectional study.
Place and Duration of Study: Rheumatology Department Pak-Emirates Military Hospital (PEMH) Rawalpindi Pakistan, from Jun 2019 to Jan 2020.
Methodology: Patients assumed to be suffering from spondyloarthritis (Spa), reporting for routine follow-up at subject OPD, were enrolled. Socio-demographic and clinical variables were measured with HLA-typing.
Results: Among 550 subjects; age and BMI scores were 31.15±10.399 (18-63 years) and 23.39±4.19 (17.2-35.0 kg/m2), respectively. 391 (71.1%) patients were found positive for HLA-B27, which was significantly more amongst 20-40 years aged (p=0.003), those with non-professional education (p=0.003), associated with raised CRP(C-reactive protein, p<0.001) and ESR(erythrocyte sedimentation rate, p<0.001), with 3-6 years since the onset of symptoms (p<0.001), up to 2 years delay in diagnosis(p<0.001), peripheral arthritis(p 0.008), having co-morbidities (p=0.011), less DAL (daily activities of life, p<0.001) with no significant impact of gender, SEC (socio-economic class), pain severity, co-morbidities and formal exercise. Severe pain was stated more by females (p=0.008), low SEC (p=0.003) and overweight patients with BMI 25-29.9 (p=0.001)
Conclusion: There is a strong association between HLA-B27 and spondyloarthritis (Spa), predominance in the 2nd and third decade, and no gender predilection. Auxiliary exploration would be valuable to recognize the predominant subtypes of the HLA-B27 allele in Pakistani patients with spondyloarthritis (Spa).

Keywords: Ankylosing spondylitis (AS), HLA-B27, Spondyloarthritis (SPA).

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INTRODUCTION

Spondyloarthritis (SpA) is a collection of inter-related but phenotypically discrete, seronegative, chronic, multisystem inflammatory ailments with diverse clinical manifestations and involvement of several different structures, principally the sacroiliac (SI) joints and the axial skeleton,[1] having relatively better outcome than rheumatoid arthritis.[2] SpA family consists of the following: Ankylosing spondylitis (AS) being the prototype, Nonradiographic axial Spondyloarthritis (nr-axSpA), Peripheral Spondyloarthritis, Spondyloarthritis accompanying psoriasis or psoriatic arthritis, Spondyloarthritis related to inflammatory bowel disease (Crohn's disease and ulcerative colitis), Juvenile-onset Spondyloarthritis and Reactive arthritis.[3] These can be further classified in accordance with predominant joint distribution as axial-SpA or peripheral SpA.[4]

In this study, HLA-B27 patients depicted no gender disparity with a surge among 20-30 years old subjects; literature reveals male predilection of 3:1, with a peak age of onset in the third decade.[5] The variation in the prevalence of spondyloarthritis (SpA) depending upon the genetic background is 1.0% in Europe. In contrast, HLAB-27 prevalence is 0.17%, 0.1% and 0.07% in Asia, South America and Africa, respectively, similar to ethnic predominance among respondents belonging to Punjab, KPK and GB in this study.[6]

The central elements for the pathogenesis of SpA are; the interface of specific genomic background amongst the gut microbiome,[7] innate lymphoid cells (ILC), and mechanical strain at the target anatomic structures (axial skeleton and its enthesis for axial-SpA and peripheral joints for peripheral-SpA.[8] The key mediators at local sites are tumour necrosis factor-alpha (TNF-a), Cyclooxygenase (COX) and interleukin 17A (IL-17A). Familial and heritability solid evidence has been revealed in these patients, exposing prime single genetic input from the gene for human leukocyte antigen B27 (HLA-B27).[9] However, its existence is not inexorable, as 8% of normal individu also depict it.

In Pakistan, there is a scarcity of statistics on the occurrence of the HLA-B27 among diagnosed Spondyloarthritis (SpA) cases. However, HLA-B27 frequency

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studies among suspected cases have been conducted earlier. In our centre, suspected Spondyloarthritis (SpA) patients were reported from all over the country for diagnosis and management. In this study, 500 confirmed Spondyloarthritis (SpA) patients were included to observe the existence of HLA-B27 and its prevalence among different ethnic groups over 12 months.

METHODOLOGY

This cross-sectional study was conducted at Rheumatology Department Pak-Emirates Military Hospital (PEMH) Rawalpindi Pakistan from June 2019 to January 2020, preceded by formal approval by the Ethical Review Board and informed consent by participants. The sample size was calculated via the WHO calculator, keeping a 95% confidence level, absolute precision of 0.05 and anticipated population proportion of 0.25.[10] Non-probability consecutive tech-nique was employed.

Inclusion Criteria: Patients (aged >17 years) of both genders, suffering from spondyloarthritis (SpA), reporting for routine follow-up at OPD, were included in the study.

Exclusion Criteria: Patients with less than three months history of inflammatory pattern backache, the onset of ailment beyond 45 years of age, or symptomatic patients meeting radiological criteria for Sacroiliitis were all excluded from the study.

HLA-B27 allele screening (by Certified protocol of PCR) was performed on patients suspected of Spondyloarthritis (SpA), not meeting the radiological criteria for sacroiliitis, and being referred to the Rheumatology Department from all over Pakistan. The subsequent diagnosis was made using the Assessment of SpondyloArthritis International Society (ASAS-2013),[11] modified Berlin algorithm.[12] Body mass index (BMI) was calculated via the latest WHO calculator for BMI, dividing patients into groups as under-weight(<18.5), normal (18.5-24.9), over-weight (25-29.9) and obese (30 or more).[13]

First 550 respondents meeting the inclusion and exclusion criteria were enrolled in the study. Documents for every respondent were filled out by the attending physician. Statistical analysis was done by SPSS-21. Quantitative data (Age and BMI score) was computed as mean ± SD (minimum-maximum), while frequency (percentage) described the qualitative variable (gender, BMI classes, ethnicity, diagnostic delay, peripheral arthritis, severity of pain and inflammatory markers). Chi-square test was applied; the *p*-value ≤0.05 was considered significant.

RESULTS

Among 550 subjects, age and BMI scores were 31.15±10.399 (18-63) and 23.39±4.19 (17.2-35.0), respectively, while 391 (71.1%) were positive for HLA-B27. Table-I illustrated relevant socio-demographic, clinical and inflammatory marker details of the respondents; significant *p*-values have been highlighted. HLA-B27 was significantly more amongst 20-40 years aged group (p=0.003), BMI (Body mass index) 18-24.[9] (p<0.001), mild-moderate DAL (daily activities of life, p<0.001), raised CRP (C-reactive protein, p<0.001) and ESR (erythrocyte sedimentation rate, p<0.001), 3-6 years since the onset of symptoms (p<0.001), up to 2 years delay in diagnosis (p<0.001), peripheral arthritis (p=0.008).

At the same time, those with professional education had a significantly more trend toward negative HLA-B27 (p=0.003). Gender, pain severity, comorbidities, and formal exercise did not significantly impact subject results. Figure-I demonstrated that HLA-B27 positive is more common in the 2nd and third decades of life, while HLA-B27 negative patients are less consistent and more variable in age.

The association between pain severity and various variables was endorsed in Table-II. Following groups stated severe pain; Females (p=0.008), low SEC (socio-economic class, p=0.003), education up to 10 years (p=0.001), BMI 25-29.[9] (p=0.001), co-morbidities like gout/diabetes mellitus/hyperlipidemia (p<0.001) with no significant difference among various age groups. Figure-2 elucidates that correspondents with severe pain had higher BMI scores than the rest.

DISCUSSION

The spA has eleven core clinical features; the commonest being inflammatory back pain comprising of Sinister onset backache in less than 40 years old, relieved by exercise but not with rest, and night pain improving on rising.[14,15]

Other features are arthritis, uveitis, enthesitis, psoriasis, dactylitis, and inflammatory bowel disease, prompt (within 24-48 hours) symptomatic relief with nonsteroidal anti-inflammatory drugs (NSAIDs), positive family history, and raised inflammatory markers (C-reactive protein or Erythrocyte sedimentation rate).[16,17]

Table-I: Relationship of HLA-B27 with subject parametrs (n=550)

Parameters	Sub-variables	Frequency	Percentage	Positive	Negative	*p*-value
Age (Years)	<20	47	8.5	28	19	0.003
	20-40	444	80.7	328	116	
	41-60	19	3.5	15	4	
	>60	40	7.3	20	20	
Gender	Male	346	62.9	246	100	0.996
	Female	204	37.1	145	59	
Education (Grades)	<5	65	11.8	40	25	0.003
	5-10	182	33.1	129	53	
	11-16	247	44.9	191	56	
	Professional	56	10.2	31	25	
Socio- Economic Class	Low	148	26.9	102	46	0.137
	Middle	351	63.8	258	93	
	Upper	51	9.3	31	20	
Body Mass Index	<18.5	127	23.1	102	25	<0.001
	18.5-24.9	242	44.0	193	49	
	25.0-29.9	136	24.7	71	65	
	30 or more	45	8.2	25	20	
	Nil	373	67.8	273	100	
Formal Exercise	Nil	142	25.8	100	42	0.925
	Walk/ Jog	250	45.5	181	69	
	Swimming	127	23.1	89	38	
	Other	31	5.6	21	10	
Daily Activities of Life	Minimal	166	30.2	125	41	<0.001
	Moderate	288	52.4	230	58	
	Severe	96	17.5	36	60	
Onset of symptoms (Years)	Up to 2	142	25.8	92	50	0.003
	3-6	405	73.6	299	106	
	7-10	3	.5	0	3	
Delay in diagnosis (Years)	Up to 2	320	58.2	276	44	<0.001
	3-6	138	25.1	66	72	
	7-10	66	12.0	31	35	
	>10	26	4.7	18	8	
Peripheral Arthritis	No	212	38.5	137	75	0.008
	Yes	338	61.5	254	84	
Pain Severity	Mild	162	29.5	108	54	0.169
	Moderate	226	41.1	170	56	
	Severe	162	29.5	113	49	
Early Morning Stiffness	Mild	290	52.7	190	100	0.003
	Moderate	162	29.5	131	31	
	Severe	98	17.8	70	28	
Co- Morbids	Gout	41	7.5	31	10	0.138
	DM	35	6.4	25	10	
	HTN	68	12.4	44	24	
	Hyperlipidemia	33	6.0	18	15	
	Nil	373	67.8	273	100	
C-Reactive Proteins	Raised	487	88.5	377	110	<0.001
	Normal	63	11.5	14	49	
Erythrocyte Sedimentation Rate	Raised	470	85.5	349	121	<0.001
	Normal	80	14.5	42	38	

A similar study, piloted at the Aga Khan University, stated an overall HLA-B27 prevalence of 1.3%, without citing ethnicities.[15] In another study, it was concluded that the Pathans (9.4%) and Kalash (4.2%) have a comparatively higher frequency of HLA-B27 than the rest of the population; however, Punjabis were not included in this study. Another study reported the frequency of HLA-B27 in the Gujjar (Punjabis) as 2.1%.[16]

Diagnostic criteria employed in this study were adapted from the stratagem denoted as the 2013 Assessment of Spondyloarthritis International Society (ASAS) modified Berlin algorithm.[10] A comprehensive history was obtained from each partaker. A thorough physical examination comprises spinal range of motion, heels for enthesitis, joints for arthritis, fingers and toes for dactylitis, and skin and eyes examination for extra-articular features, including psoriasis and uveitis, was carried out. Inflammatory markers, including C-reactive protein (CRP) or an erythrocyte sedimentation rate (ESR), were also acquired in patients suspected of axial Spondyloarthritis (axSpA) to confirm the diagnosis.[11] The modified ASAS algorithm has about 75 to 80 percent sensitivity and specificity for axial Spondyloarthritis (axSpA).[18]

Table-II: Association of Pain Severity with relevant Parameters (n-550)

Parameters	Sub-variable	Mild	Moderate	Severe	*p*-value
Age (Years)	<20	16	14	17	0.162
	20-40	130	194	120	
	41-60	5	6	8	
	>60	11	12	17	
Gender	Male	111	149	86	0.008
	Female	51	77	76	
Education	<5	14	26	25	0.001
	5-10	56	64	62	
	11-16	65	122	60	
	Professional	27	14	15	
Socio-Economic Class	Low	32	71	45	0.003
	Middle	104	141	106	
	Upper	26	14	11	
Body Mass Index	<18.5	46	53	28	0.001
	18.5-24.9	54	115	73	
	25.0-29.9	52	37	47	
	30 or more	10	21	14	
Co-Morbids	Gout	21	9	11	<0.001
	DM	14	7	14	
	HTN	19	32	17	
	Hyperlipidemia	5	5	23	
	Nil	103	173	97	

The human leukocyte antigen (HLA) complex is equivalent to the human major histocompatibility complex (MHC), relating a cluster of genes on the sixth chromosome that inscribe a range of antigen-presenting molecules, cell surface markers as well as other proteins, principally employed in immune function.[19] More than 200 genes comprises the classical MHC, spanning 3.6 megabases (Mb) and subdivision in three regions: Class-I, Class -II, and Class-III.[20] HLA-A, B, and C are the "classical" Class-I HLA antigens encoded by genes in the Class-I region. These antigens are exhibited by virtually the entire body's cells, excluding the trophoblasts and red blood corpuscle. HLA-B27 is a distinct HLA Class-I surface allelic antigen variant, owing to its high affiliation with typical dissimilar amino acid configuration from other Class-I molecules like the presence of free thiol group of Cys 67 B pocket and B pockets as well as strong correlation with spondyloarthritis (SpA). It is exceedingly polymorphic and has a key part in defensive immunity against intracellular parasites comprising viruses and bacterias.[21]

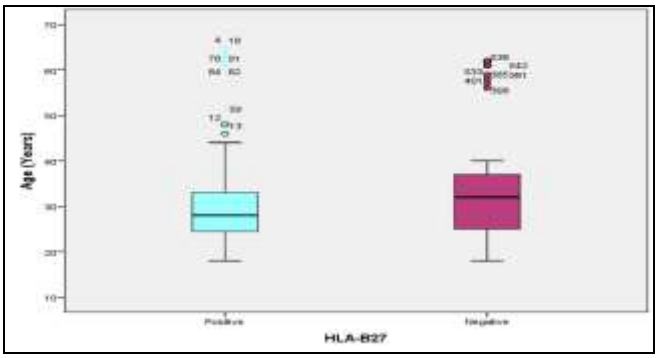

Figure-1: HLA-B27 results amongst Various Ages (n-550)

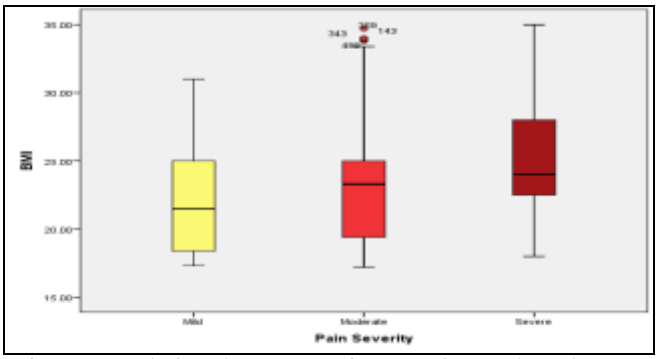

Figure-2: Relation between Pain Severity and Body Mass Index (n-550)

Genetic factors have overwhelming importance in susceptibility to spondyloarthritis (SpA). There are significantly augmented chances of developing Ankylosing spondylitis in blood relatives, with First, second, and third-degree relatives having relative risks of 94%, 25%, and 4%. The mode of inheritance is polygenic with multiplicative interaction among loci.[22] The relationship with the HLA-B27 gene comprising at least 213 subtypes, first recognized in 1973, has the strongest association with the disease with the overall contribution of 16 to 50 percent of the total genetic risk. HLA-B27 exists in approximately 80 to 95 percent of Ankylosing Spondylitis patients in most ethnic groups.

Approximately 40 to 50% of sacroiliitis, Crohn's disease and psoriasis patients have positive test reports for HLA-B27.[23]

The mechanism by which HLA-B27 causes the development of spondyloarthritis (SpA) stayed unknown. However, numerous postulates have been suggested to define its role in the pathogenesis of the disease. The arthritogenic peptide hypothesis undertakes that the cross-reactivity of cytotoxic T cell lines (CTLs) originates from molecular mimicry amongst pathogens and self-peptides, resulting in spondyloarthritis (SpA). In contrast, the HLA-B27 misfolding hypothesis articulates that the build up of anomalously folded HLA-B27 in the endoplasmic reticulum triggers an intracellular signal, causing unfolded protein response and stress to the endoplasmic reticulum. An additional hypothesis narrates the abnormal immune response leading to the formation of HLA-B27 homodimer on the cell surface, specific receptors identified as the killer immunoglobulin-like receptors, expressed on natural killer and CD4+ T cells, recognize these dimers resulting in disease.

Different subtypes are associated with various subtypes of spondyloarthritis (SpA). The most frequent subtypes are HLA-B27 04 and HLA-B27 05. HLA-B27 09 and HLA-B27 06 are the only two subtypes not considered to be linked with spondyloarthritis (SpA). Of many documented HLA-B27 alleles, HLA-B 27:05 has the strongest relationship with Ankylosing Spondylitis amongst the Japanese and HLA-B27:04 among Chinese.[21,24]

Only 1 to 5 percent of individuals who tested positive for HLA-B27 develop Ankylosing Spondylitis suggesting that other genetic factors are also important in disease susceptibility. Non-MHC variants contribute nearly 7% of the heritable risk. Non-MHC variants include Tumor necrosis factor gene family, lymphotoxin beta receptor (LTBR), and endoplasmic reticulum amino peptidases that encode genes termed ERAP1 and ERAP2, and tumour necrosis factor receptor 1 (TNFRSF1A).[24] The presence of subclinical bowel disease in Ankylosing Spondylitis (AS) and its connection with inflammatory bowel diseases (IBD) may be explained by T lymphocyte activation and differentiation of CD4+ or CD8+ T lymphocytes as well as sharing of 65 genes with Crohn disease, ulcerative colitis, and celiac disease.[19]

71% of the individuals included in this study were HLA-B27 positive, out of which 62.9% and 37% were males and females, respectively, which is consistent with previous studies' findings, reporting that spondyloarthritis (SpA) are predominantly seen in males. Auxiliary investigative studies to define the predominant subtypes of this allele and their prevalence among Pakistani patients with spondyloarthritis (SpA) would be valuable.

Despite our study's limitations, the outcomes showed that the frequency of HLA-B27 is relatively high among Pakistani spondyloarthritis (SpA) patients compared to other regional studies. Furthermore, the HLA-B27 positive group has more severe symptoms of arthralgias and has more incidence of peripheral arthritis than the negative group. However, before making a definite conclusion, numerous features such as ethnic upbringing, topographical differences, and general environmental aspects should be reflected upon. Therefore, auxiliary far-reaching and all-encompassing studies on established spondyloarthritis (SpA) patients are compulsory to gauge the prevalence of HLA-B27 midst of dissimilar ethnic groups and to classify principal subtypes of HLA-B27 among our population.

CONCLUSION

There is a strong association between HLA-B27 and spondyloarthritis (SpA), predominance in the 2nd and third decade, and no gender predilection. Auxiliary exploration would be valuable to recognize the predominant subtypes of the HLA-B27 allele in Pakistani patients with spondyloarthritis (SpA).

Conflict of interest: None.

Author's Contribution

AJ: Direct contribution, AF: Supervision, NA:, BA:, KA:, AJ: Intellectual contribution.

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