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HLAB27 PROFILE IN ALGERIAN PATIENTS WITH ANKYLOSING SPONDYLITIS

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Key words: *Ankylosing spondylitis (AS) , Human Leukocyte Antigen B27 (HLAB27), age onset of disease, morning stiffness, uveitis, disease activity*

INTRODUCTION

Ankylosing spondylitis (AS) is the prototype of a group of chronic inflammatory diseases known as spondyloarthritides (SpA) (Alam et al., 2017) .In AS, the axial skeleton, sacroiliac joints, and, to a lesser extent, peripheral joints and various extra-articular organs, such as the eyes, skin, and cardiovascular system, are characterized by inflammation (Kim & Kim, 2010). AS is a disorder, also, defined by a high relationship with Human Leukocyte Antigen (HLA) B27 (REGISPONSER et al., 2018). This later is found in just 8% of the general population globally (Abdelrahman et al., 2012). It was found that (HLAB27–) (SpA) patients had a later average age at illness start than (HLAB27+) (SpA) patients (Feldtkeller et al., 2003). Several studies have attempted to determine the prevalence of AS; variations have been seen based on the population investigated, with a decreasing North-South gradient in general. The regional distribution of the (HLAB27) allele, the key contributor in illness risk, explains these discrepancies. The subarctic areas of Eurasia and North America have the highest incidence of (HLAB27) and AS. In South America, Australia, and Africa, (AS) is essentially non-existent (Dahmani et al., 2017).

(SpA) is uncommon in Africa, particularly in Sub-Saharan Africa, where (HLAB27) frequency is extremely low, if not non-existent. However, the illness occurs as a result of ethnic mixing, and its frequency varies from nation to country. In Nigeria and Zimbabwe, the prevalence of (AS) is 0%, whereas in South Africa it is 0.15 percent (Dahmani et al., 2017).

The frequency of the (HLAB27) allele is significantly greater in the Maghreb countries than in black African countries. (HLAB27) positivity (+) was found in 59 percent of (AS) patients in Morocco and 62 percent of (AS) patients in Tunisia. In Algeria, similar proportions were discovered, with 63 percent in the Center region and 52 percent in the West region (Dahmani et al., 2017).

The current study's aim was to examine (HLAB27)'s profile and to analyze its effect on Algerian patients with Ankylosing Spondylitis.

MATERIALS AND METHODS

Population:

Our survey covered 291 patients diagnosed with ankylosing spondylitis at the Functional Rehabilitation department of Hassani Abdelkader University Hospital of Sidi Bel Abbes region (Western Algeria), between 2018 and 2021. We assessed a set of factors, including gender, age, disease duration, morning stiffness, medical history, articular and extra-articular injuries, laboratory data, favorable outcomes, (AS) patients' (HLAB27), disease activity markers, and treatment.

Statistical Analysis:

The differences between groups of HLAB27 + and HLAB27- were analyzed by the Chi- square test for qualitative variables and the independent sample t-test for quantitative variables. Values are expressed as number (percentage) or mean ± standard deviation.

Statistically significant differences were maintained when the p-value was less than or equal to 0.05 ($p \leq 0.05$). All data were processed and analyzed via SPSS 22.0 (Statistical Package for the 44 Social Sciences, IBM Corporation; Chicago, IL. August 2013).

RESULTS AND DISCUSSIONS

Two hundred and ninety-one (291) patients with a confirmed diagnosis of AS were included in our study. 124 (42.8%) were men and 166 were females (57.2%) with a sex ratio F/H of 1.33. The average age was 38.27±12.04 ranging from 17 to 82 years old. 70.79% (n=206) of cases were (HLAB27) positive, while 29.20% were (HLAB27) negative.

Table 1 and 2 shows a comparison of the demographic, clinical, paraclinical and therapeutic characteristics of 2 groups (positive (HLAB27) and negative (HLAB27).

The mean age of (AS) patients was 36.68±11.26 years in group of (HLAB27+) vs 39.01±12.36 in group of (HLAB27-); we found a significant association between (HLAB27) positive and age p=0.041 and disease age onset p=0.001. Actually, the mean age of disease age onset was earlier in (HLAB27) positive group than (HLAB27) negative group (29.46±8.99 VS 31.89±10.98 years). Concerning, the duration morning stiffness, the difference between the both group was close to the significance level (p=0.052). However, we did not found any relation between (HLAB27) antigen and some epidemiological factors such as: sexe, disease duration, spine damage, medical history and radiological joint damage (p>5%).

The association between (HLAB27) and ankylosing spondylitis remains the strongest known linkage between a major histocompatibility complex (MHC) antigen and the disease (Sheehan, 2004).

This study was conducted to assess the prevalence and effect of (HLAB27) among patients with (AS) living in Algeria. 70.79% of cases were (HLAB27) positive; the mean age of (AS) patients was 36.68±11.26 years in group of (HLAB27+) vs 39.01±12.36 in group of(HLAB27-) (p=0.041) comparable to those found by Jung et al (2019) who noted an average age of 38.83 ± 12.66 (HLAB27+) vs 38.48 ± 14.17 years (HLAB27-) (p= 0.761).

We did not find a significant association between positive (HLAB27) and gender (P=0.643) which match with the results of REGISPONSER et al (2018) p=NS, Kim & Kim (2010) p=NS and Freeston et al (2007) p = 0,103. Male predominance in the (HLAB27+) was seen in several investigations : Yang et al (2013) found 80.2% of male patients with positive (HLAB27) vs 72.4% with negative (HLAB27) p<0.001 and Jung et al (2010) found (94.8) vs (87.3%) with p=0.016 . However, in our study, whether (HLAB27) was present or not, we noted a dominance of female patients (57.2%) with a sex ratio F/H of 1.33. This difference in gender affection can be explained by the fact that our survey was carried out in a single rehabilitation center. James (1991) suggested a connection between high levels of testosterone in males and the (HLAB27) antigen. In this case, (HLAB27) antigen could be able to identify males who have (AS) and provide a prognosis score (Akassou & Bakri, 2018).

In our study, the disease age onset was earlier in (HLAB27) positive AS patients with p=0.001 which is in agreement with REGISPONSER et al (2018) p<0.001 and Kim & Kim (2010) p=0.002, but not with Alam et al (2017) p=0,07, Awada et al (2000) and Qian et al 2017 p= 0,10 findings.

The onset of (AS) might be brought on by abnormal peptide presentation, misfolded (HLAB27) molecules, (HLAB27) dimers, or β2m accumulation and deposition (Chen et al., 2017).

Moreover, the analyses of Akassou & Bakri, (2018) showed that (HLAB27) patients have a younger age of onset. Other research surveys looked at the age of onset and found that late-onset (AS) patients had lower rates of (HLAB27) positive, lower levels of inflammatory markers, delayed diagnosis, and decreased utilization of methotrexate and anti-tumor necrosis factor medication.

Fascinating aspect of (AS) is the correlation between the age of onset and (HLAB27) positive, this may be used as a predictor of the course and prognosis of the disease (Akassou & Bakri, 2018). But this was not the case with the disease duration parameter as we reported no association with (HLAB27) p=0.099 which is similar to Kim & Kim (2010) (p=NS) and Jung et al (2019) 5.09 ± 5.74 vs 3.45 ± 2.68 (p=0.343) findings. Unlike, other authors who found different findings such as REGISPONSER et al (2018) (p=0.038), Awada et al (2000) (p=0.06) and Freeston et al (2007) who reported that (HLAB27+) patients with (AS) have significantly longer disease duration than (HLAB27-) with (p= 0,012).

In our population, the association between morning stiffness and (HLAB27) was close to the significance level (p=0.052); while, this association was not significant in Awada et al (2000) research study (p=NS) on a Lebanese population.

As stated by REGISPONSER et al (2018) and (Alam et al., 2017), spine injury was not significantly related with (HLAB27), p=NS, p=0,8 respectively, which concords with our findings. In our series, the lumbar joints were affected by (AS) in the majority of individuals whether (HLAB27) was present or not. No differences in axial symptoms was reported (cervical p=0.963, lumbar p=0.228). According to Yang et al (2013) (AS) patients who carry the (HLAB27+) gene have noticeably greater symptoms of spinal column involvement (lumbar spine and thoracic spine).

(HLAB27) has been shown to have a significant impact on the frequency and severity of extra-articular/musculoskeletal symptoms of inflammatory diseases, such as diagnoses of ophthalmic, cardiac and respiratory disorders. Indeed, patients with positive (HLAB27) are more likely to develop acute anterior uveitis than (HLAB27) negative (Kim & Kim, 2010)which was underlined by our findings (AS) at 35.4% but with no significant association between (HLAB27) and uveitis (p=0.549); indistinguishable to REGISPONSER et al (2018) p=NS, Awada et al (2000) p=NS, Alam et al (2017) p=0.11, Freeston et al (2007) p=0.661; but unlike to Kim & Kim (2010) and Jung et al (2019) who noted a significant association between (HLAB27) and uveitis with (p=0.001) and (p=0.004) respectively. Regional variations in (HLAB27) prevalence may explain the variability prevalence of anterior uveitis. The pathophysiology of (HLAB27+) Acute Anterior Uveitis has been linked to Salmonella, Shigella, Campylobacter, Klebsiella, Yersinia, or Chlamydia

trachomatis. It has been established that the putative "uveitogenic" peptides produced by these bacteria possess the essential sequences to bind and to present to T cells through (HLAB27). According to some author's theory, these microbe-derived antigens may cause CD8+ T-cell immune reactions that cross-react with self-tissue antigens that are only present in the joint or uvea, causing autoimmune tissue inflammation (Chang et al., 2005).

It has been suggested by Rudwaleit et al that (HLAB27+) AS patients respond better to anti-TNFα treatment, which could be due to the fact that these patients express more TNFα in the inflammatory sites (Rudwaleit, 2004). Höhler et al (1998) found that allelic variations in the TNFα promoter region influence susceptibility to disease development in (HLAB27)+ subjects, there may be a link between various clinical manifestations and (HLAB27) status in (AS) patients. As reported by certain research studies, (HLAB27) is linked to a greater frequency of uveitis and cardiac involvement in (AS) patients (Akassou & Bakri, 2018). Further studies showed that the (HLAB27+) (AS) group had a higher prevalence of uveitis/iritis and a poorer visual prognosis compared to their (HLAB27-) patients such as Yang et al (2013) 9.5% VS 6.9%, Power (1998) 90% VS 60%, D'Ambrosio et al (2017) and confirmed by our findings 35.4% VS 31.8%. Likewise for psoriasis where any association with (HLAB27) was found in our series with p=0.174 as the results of Awada et al(2000) p=NS and Qian et al (2017) p=0.08, but opposed to REGISPONSER et al (2018) p<0.0001.

The studies of REGISPONSER et al (2018) (p=NS), Qian et al (2017) (p=0,91), Alam et al (2017) (p=0,39) did not reported a significant association between ESR titer (mm/h) and (HLAB27); whereas, in our study this relationship was close to the significant level with p=0.052.

However, for accelerated ESR we reported a significant association p=0.004.Furthermore; CRP titer (mg/l) p=0.799 was not significant as found in findings of REGISPONSER et al (2018) p=NS and Alam et al (2017) p=0.71 but it was not the case for results Qian et al (2017) (p=0.01).

A close significant relationship between positive CRP and (HLAB27) p=0.051 was reported in our series; while, Qian et al (2017) reported a significant association p=0.04 which can be explained by patients with clinically active illness that may not have high inflammatory markers. many studies showed that high inflammatory indicators including a greater erythrocyte sedimentation rate and C-reactive protein may signify severity based on the presence of (HLAB27) antigen (Burton et al., 2007) and (Linssen, 1990).

In our study, the number of smokers was 25(12.1%) in group of (HLAB27+) vs 3(3.5%) in group of (HLAB27-). We noticed that tobacco was significantly associated with (HLAB27) p=0.024 which is similar to the findings of Jung et al.(2019)55.9% vs 6.5% p= 0.001.

According to recent studies, tobacco might contribute to the emergence of autoimmune diseases. Smoking may play a major role in the development of inflammatory rheumatic disorders like ankylosing spondylitis (Chen et al., 2013). Moreover, many researchers have shown that smoking and ankylosing spondylitis have a convoluted relationship (Mattey et al., 2011). Many research confirmed that HLA-B27 positive patients demonstrated increased disease activity with smoking and suggesting that stopping smoking is a mandatory step in controlling the disease activity and having favorable outcome (Farouk et al., 2021). (Ciurea et al., 2013) cited that Tobacco smoking is associated with increased disease activity in HLA-B27 positive axial spondyloarthritis patients, but does not alter the course of disease activity).We did not find a correlation with (HLAB27) antigen for radiologic joint damage (knees p=0.172, hips p=0.219), which is comparable to Kim & Kim (2010) about knees results p=NS but this was not the case with the hips (p=0.03) in Korean population.

In chinese Ankylosing Spondylitis patients, Yang et al (2013) found a higher frequency of hip joint involvement in (HLAB27+) (AS) comparing to (HLAB27−) (AS).

Our findings back up the link between (HLAB27) and disease activity, as our results demonstrated a relationship between disease activity indices and (HLAB27) antigen, it seemed to have a significant role in the development of AS; (BASDAI) and (ASDASCRP) scores were considerably higher in (HLAB27) positive (AS) patients.We recorded also an association between (HLAB27) and (BASDAI) p<0.0001 and (ASDASCRP) p=0.007 which is similar to REGISPONSER et al., 2018 p=0.047.

Vargas-Alarcon (2002) demonstrated that (HLAB27+) patients had higher Bath indices for disease activity 4.7±2.2 5 vs 3.6± 2.4 (p=0.006), Popescu et al(2014) found that HLA B27 positive patients had a median (BASDAI) higher than HLA B27 negative patients (p = 0.033), in reverse to (Alam et al., 2017) (p=0,67), (Qian et al., 2017) (p=0,93) and (Freeston et al., 2007) (p=0.658) findings. Thus, more severe clinical course can be observed in (HLAB27+) AS patients.

In our survey, (HLAB27+) patients were treated with No Steroidal Anti-inflammatory drugs (NSAIDs) and biotherapy more frequently, which indicates a higher level of activity and severity of (AS). We demonstrated a relation between (HLAB27) and No Steroidal Anti-inflammatory drugs (NSAIDs) treatment p=0.042; same results were observed in the study of Freeston et al (2007) p=0,025, but not in accordance with those previously published by Alam et al (2017) p=0,18 and Jung et al (2019) p=0.771. Concerning methotrexate and

sulfasalazine, we did not find a relation with (HLAB27) p=0.064 , p=0.065, similar to Jung et al(2019) p=0.323, p=1.000 respectively.

Moreover we did not find a relation between (HLAB27) and biotherapy, same results were reported by other studies Jung et al., 2019;Alam et al., 2017; Freeston et al., 2007; Qian et al., 2017) .

Nonetheless our study had a set of limitations as there were relatively few patients included in the study, and there were some differences in patient numbers between the groups and the prevalence of clinical findings that was based on data from an only one center.

Table 1. Clinical, Radiologic, and Laboratory Data in Ankylosing spondylitis Patients Based on HLAB27

Variables	Positive (HLAB27) n= 206	Negative (HLAB27) n= 85	P value
Age	36.68±11.26	39.01±12.36	**0.041***
Sexe			0.643
Males	86(41.7%)	38(44.7%)	
Females	120(58.3%)	47(55.3%)	
Disease duration	6.91±3.63	7.18±5.28	0.099
Disease age onset	29.46±8.99	31.89±10.98	**0.001***
Duration morning stiffness	26.43 ±28.05	22.00±23.36	0.052
Spine damage			
Cervical	83(40.3%)	34(40.0%)	0.963
Lumbar	157(76.2%)	59(69.4%)	0.228
Laboratory data			
ESR titer (mm/h)	46.89 ±27.36	42.61±31.96	0.052
Accelerated ESR	178(86.8%)	62(72.9%)	**0.004***
CRP titer (mg/l)	20.37 ±21.72	17.84±26.04	0.799
Positive CRP	124(60.5%)	41(48.2%)	0.051
Tobacco	25(12.1%)	3(3.5%)	**0.024***
Radiologic joint damage			
Knees	24(11.2%)	15(17.6%)	0.172
Hips	60(29.1%)	31(36.5%)	0.219
Disease activity indices			
BASDAI	3,11±2,18	2.53±0.81	**0.0001***
ASDASCRP	2,64±1.39	2.58±1.05	**0.007***
Disease activity			
Inactive	51(24.8%)	14(16.5%)	
Moderate	41(19.9%)	21(24.7%)	**0.023***
High	88(42.7%)	47(55.3%)	
Very high	26(12.6%)	3(3.5%)	
Medical treatment			
Methotrexate	17(8.3%)	2(2.4%)	0.064
Sulfasalazine	172(83.5%)	63(74.1%)	0.065
NSAIDs	19(9.2%)	15(17.6%)	**0.042***
Biological treatment			
Humira	172(83.5%)	69(81.2%)	0.634
Remicade	21(10.2%)	3(3.5%)	0.060
Enbrel	11(5.3%)	10(11.8%)	0.054

Table 2. Comorbidity profile of our patients

Variables	Positive (HLAB27) n= 206	Negative (HLAB27) n= 85	P value
Uveitis	73 (35.4%)	27(31.8%)	0.549
Psoriasis	9 (4.4%)	1(1.2%)	0.174
Crohn's disease	3 (1.5%)	2(2.4%)	0.592
Diabetes	3(1.5%)	2(2.4%)	0.592
Renal failure	2(1.00%)	1(1.2%)	0.875

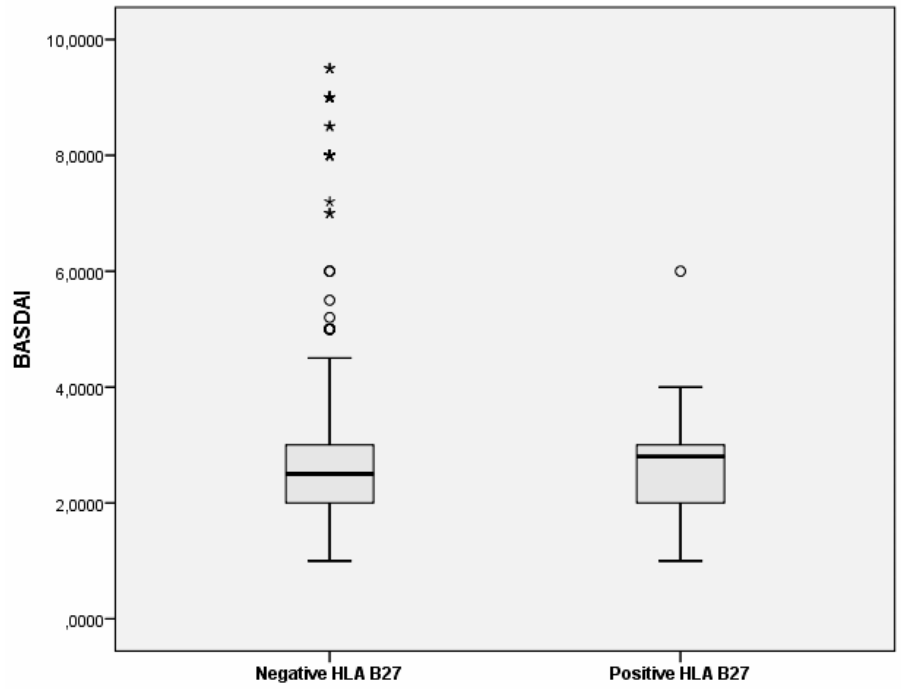

Figure 1. Association between (BASDAI) and (HLAB27)

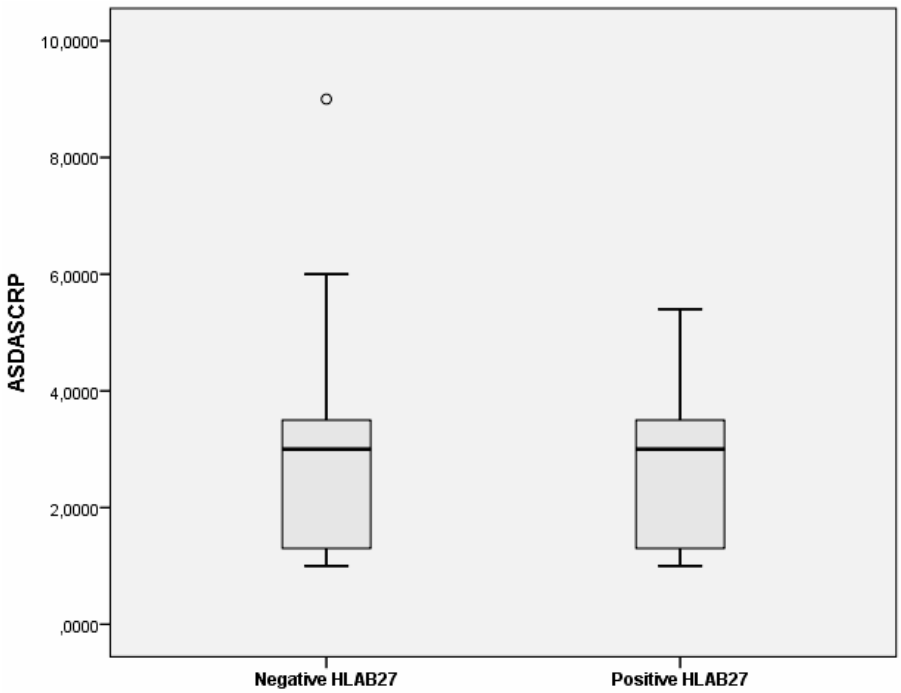

Figure 2. Association between (ASDASCRP) and (HLAB27)

CONCLUSIONS

The HLA B27 test is requested to help, reinforce or confirm a suspected diagnosis of ankylosing spondylitis. Our data showed that the majority of (AS) Algerian patients positively expressed the HLAB27 antigen and seem more suffering from morning stiffness, high disease activity indices, high level of accelerated ESR and extra-articular damage. Additional research with a larger patient population is required, as well as

research on the prevalence of (HLAB27) in healthy Algerian population.

ABSTRACT

Our objective was to see if there were any differences between (HLAB27–) and (HLAB27+) individuals with ankylosing spondylitis in Western Algeria.291 patients diagnosed with (AS) at the level of rehabilitation department of (Sidi-bel-Abbes University Hospital) were enrolled. The studied parameters were: age, gender, disease duration, age onset of disease, morning stiffness, joint and extra-articular injuries, laboratory data, disease activity, and treatments. All data were processed and analyzed via EXCEL and SPSS 22.0 (Statistical Package for the 44 Social Sciences, IBM Corporation; Chicago, IL. August 2013). Most of patients were HLAB27positive (70.79%), the mean age of disease age onset was earlier in the (HLAB27) positive group 29.46±8.99 VS 31.89±10.98 years (p= 0.001) and the morning stifness was higher in the (HLAB27) positive group 26.43 ±28.05 VS 22.00±23.36 Min. Moreover, patients with positive (HLAB27) suffer from uveitis more than patients with negative (HLAB27) 72(35.4%) VS 27(31.8%), the inflammatory parameters was higher in HLAB27 positive group and Smoking was mostly noted in this group of patients (P=0.024). Disease activity indices were significantly greater in group of positive (HLAB27) with (BASDAI) p=0.019, (ASDASCRP) p=0.007. Regarding medical treatment, Sulfasalazine and Humira were the most commonly used drugs for both groups .The presence of the (HLAB27) antigen is linked to an early start of ankylosing spondylitis in Algerian patients, as well as a high incidence of uveitis, inflammatory parameters, and disease activity indices.

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