Original Paper

The Importance of HLA-B27 in the Evolution of Reactive Arthritis

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ABSTRACT: Reactive arthritis is an inflammatory joint disease which develops after 1-4 weeks following an enteral, genital or ORL infection, with a higher frequency in HLA-B27 positive patients. AIMS: The objective of this paper is to study the importance of HLA-B27 antigen in the development of reactive arthritis. Patients and methods. The transversal, observational study was conducted in the Rheumatology Clinic of the University of Medicine and Pharmacy of Craiova during the period 2012-2015 and included 112 patients. They were divided into three groups, as follows: group I (52 reactive arthritis cases), group II (30 other spondyloarthritis cases), group III (40 osteoarthritis cases). ELISA and PCR techniques were used to determine the antigen. Results. Those whom had this genetic marker present, the number of enthesitis almost doubled highlighting a possible correlation between the antigen and these imaging changes. We can confirm the same thing for the erosions as well. Unlike enthesitis, erosions occurred also in group III (37.5%), but if we refer to the first two groups, we will observe a significant relationship regarding HLA-B27. More specifically, in HLA-B27 positive patients (68.97%), erosions were found to be twice as numerous than in HLA-B27 negative patients (31.03%). In group I we identified stage 2 sacroiliitis in 68% of HLA-B27 positive patients and 32% in HLA-B27 negative, which shows another link to this antigen with both joint destruction and a possible unfavorable evolution of reactive arthritis. Conclusions. This antigen specific to the seronegative group of spondyloarthritis determines the acceleration of articular destruction, translated by erosion, and the evolution of sacroiliitis to a more advanced stage.

KEYWORDS: *Reactive arthritis, HLA-B27, sacroiliitis, erosions*

Introduction

Reactive arthritis (ReA) is part of the seronegative spondyloarthritis (SpA) group and it is characterized by an inflammatory joint disorder that occurs 1-4 weeks after an enteral or genitourinary infection and is more common in HLA-B27 positive patients. One of its features, which distinguishes it from infectious arthritis, is that there is no evidence of pathogenic microorganisms in the joint fluid or synovial membrane. The HLA-B27 profile is the genetic feature of SpA, the phenotype being found in about 90% of the cases with AS and in 60-70% of the cases with reactive arthritis [1,2,3].

On the other hand, according to population studies, in HLA-B27 negative patients, the disease has a mild evolution with rare extraarticular manifestations and a better long-term prognosis [4].

The mechanism of intracellular replication of *Salmonella* depends on the unique characteristics of the B component from the HLA-B27 molecule, especially the glutamic acid section in position 45. It appears that the modulating effects of the HLA-B27 molecule depend on the type of studied cell and the used trigger. What remains incompletely understood is the origin of susceptibility to SpA and implicitly to ReA, either deriving from the non-antigenic effect of HLA-B27 or altering the effects of antigens.

Viral infections have once again underlined the importance of a thorough understanding of pathogen-host interactions. Recent studies have shown that HLA-B27 influences the outcome in a positive way for both HIV infection and HCV infection, which may indicate a possible B27 protection against HIV infection. In the case of HCV infection, B27 has been strongly associated with the spontaneous viral clearance, which was linked to a dominant $CD8^+$cytotoxic T lymphocyte (CTL) epitope. In conclusion, the protection given by HLA-B27 in HCV infection can be explained by the need to accumulate a mutation group within the immunodominant epitope in order to escape T cell recognition.

In the pathogenesis of SpA, an important role is their association with HLA-B27, namely the indirect involvement of class I major histocompatibility complex (MHC)-specifically $CD8^+$CTL. These $CD8^+$T cells in the synovial fluid can express natural killer (NK) cell receptors, which in turn can modulate their cytotoxicity and thus can contribute to the disease pathogenesis. The characteristics of T cells were implicated in the fact that certain HLA-B27 subtypes are more strongly associated with SpA. Thus, the HLA-B27*2709 subtype, although varying by a single amino acid

(His116-Asp110) from HLA-B27*2705 subtype (which is strongly associated with ankylosing spondylitis), is not found in patients with ankylosing spondylitis. $CD8^+$T cells have been shown to distinguish between these two B27 subtypes under the same EBV-LMP-2-derived epitope, thus suggesting that these subty3pes can be differentiated through the presence of the arthritogenic peptide derived from microbial sources [5,6].

Aim

The objective of this paper is to study the importance of HLA-B27 antigen in the development of reactive arthritis.

Material and Method

The transversal, observational study was conducted within the Rheumatology Clinic of the University of Medicine and Pharmacy of Craiova from January 2012 to December 2015.

The total number of patients enrolled in the study was 112, divided into three groups according to diagnosis, as follows (Table 1).

Table 1. Group division according to diagnosis.

Group	Number of patients	Disorder
I	52	reactive arthritis
II	30	Spondyloarthritis
III	40	Osteoarthritis

For inclusion in the study we used the following criteria (Table 2).

Table 2. Eligibility criteria for study participation.

Inclusion criteria	Exclusion criteria
Patient Participation Agreement	The confirmation of another spondylarthropathy
Certain diagnosis of ReA according to the criteria established by the European Spondylarthropathy Study Group with less than six months development	Patients with severe conditions: organ failure, B or C viral hepatitis, immunological deficiencies, active tuberculosis
Age over 18	Patients during pregnancy or lactation
Clear history of enteral or genitourinary infections	Alcohol addiction
	Severe psychiatric disorders
	Non-cooperating patients

All included patients were clinically and biologically evaluated. Data collection was performed for each patient enrolled in the study, including clinical and paraclinical evaluation such as ultrasound, X-Ray and magnetic resonance imaging (MRI).

The collected data included: general (demo-graphic, significant heredocolateral history, comorbidities), anamnestic (onset, symptoms) and behavioral aspects (Table 3).

Table 3. Collected data.

Objective Exam	General Specific
Biological Explorations	Standard tests (complete blood count, erythrocyte sedimentation rate, quantitative C-reactive protein, fibrinogen, transaminases, urea, creatinine, uric acid)
	HLA-B27 antigen (PCR technique)
	Anti-*Chlamydia trachomatis* antibody (direct immunofluorescence technique)
	IgG and IgA-Chlamydia trachomatis antibody (ELISA method)
	Anti-*Ureaplasma urealyticum* antibody (specific kit)
	Anti-*Yersinia enterocolitica* antibody (Western Blot method)
	Anti-Salmonella antibody (Widal test)
	Anti-*Campylobacter jejuni* antibody (immunoenzymatic technique)
	Anti-Shigella antibody (tube/microplate agglutination reaction)
Ophthalmologic examination	Visual acuity evaluation
	Examination of the anterior and posterior poles of the eye
	Intraocular pressure measurement
Imaging evaluation	Musculoskeletal ultrasound
	Radiological exam
	Nuclear magnetic resonance (where applicable)
Statistical analysis	Microsoft software package
	Excel data processing module (Cross, Basic Tabs, correlate, regression, Factor Analysis, Data Analysis Module, Stat 2014 Module)
	Statistical indicators (arithmetic mean, standard deviation)
	ANOVA Test
	Quark Square Test

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Results

HLA-B27 defines the genetic character of ReA, being associated with a more severe arthritis evolution, frequent extraarticular manifestations, and a prognosis of unfavorable disease.

ELISA and PCR techniques were used to determine the antigen.

As noted above, identification of this antigen in ReA can partially explain the frequency of extraarticular manifest ations.

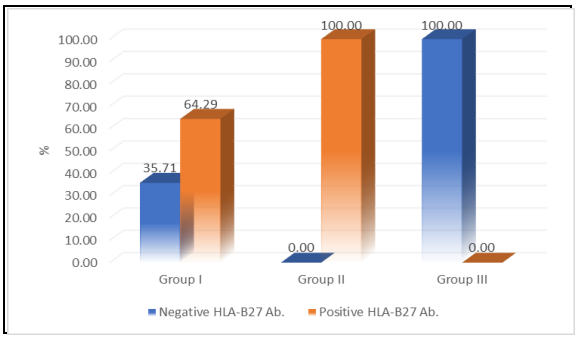

Figure 1. Group distribution regarding HLA-B27 presence.

The identification of HLA-B27 antigen showed significant differences between the three groups ($p<0.001$).

The antigen was highlighted in all patients in group II, in no patient in group III and in 64.29% of patients in group I.

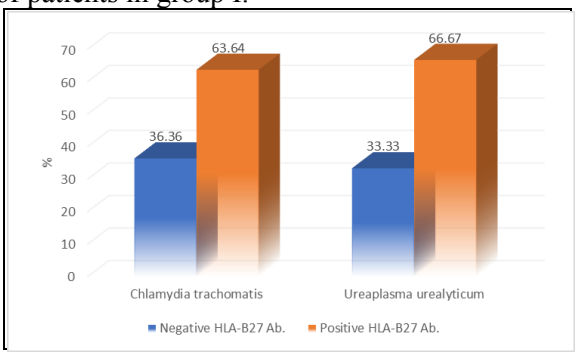

Figure 2. Relationship between pathogen and HLA-B27.

We analyzed, for the patients in group I, the relationship between the presence of the HLA-B27 antigen and the pathogen involved, but the differences were minimal ($p=0.866>0.05$).

The presence of HLA-B27 is related to the severe evolution of ReA with increased articular and periarticular destruction.

We correlated the presence of HLA-B27 antigen and the presence of erosions, enthesitis and enthesophytes.

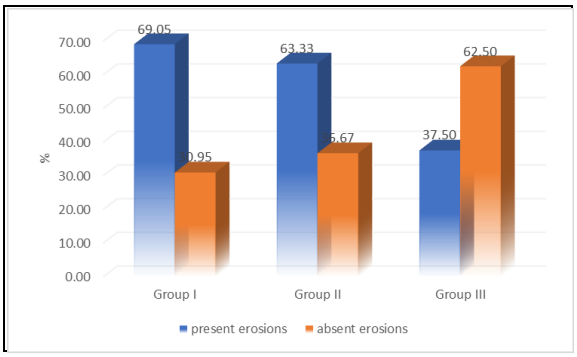

Figure 3. Group distribution regarding erosion presence.

There is a significant difference regarding the presence of erosions between the three lots ($p<0.05$)

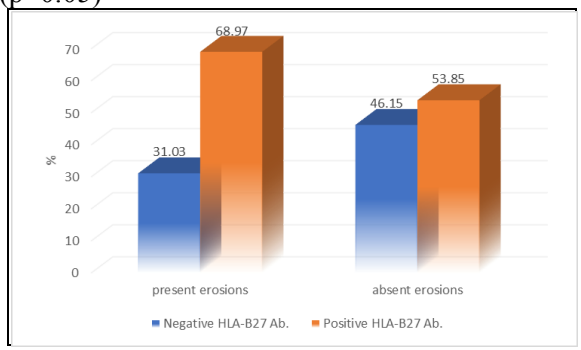

Figure 4. Relationship between erosions and HLA-B27.

By analyzing the relationship between the presence of HLA-B27 antigen and the presence of erosions for the patients in group I, we did not identify a statistically significant connection ($p=0.344>0.05$).

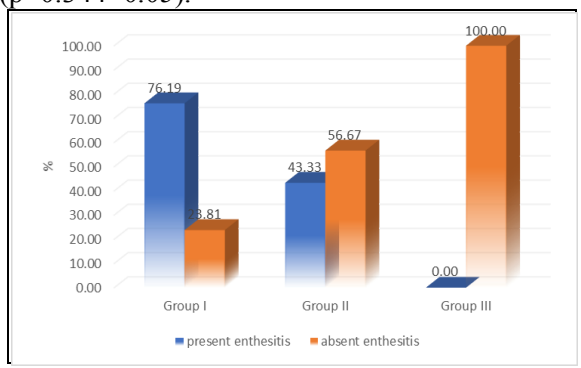

Figure 5. Group distribution regarding enthesitis presence.

The presence of enthesitis significantly differentiates the three groups ($p<0.001$), the patients in group II having none at all, while over three quarters of patients in group I are affected.

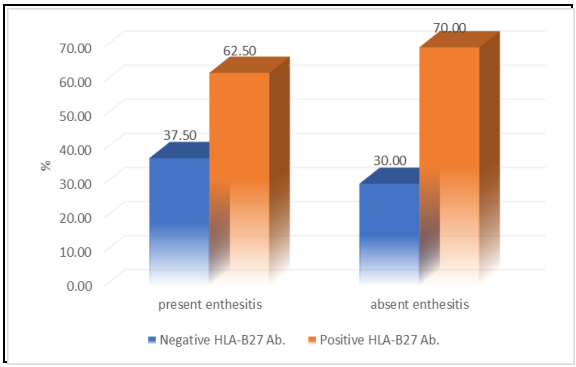

Figure 6. Relationship between enthesitis and HLA-B27.

Analyzing the relationship between the presence of HLA-B27 antigen and the presence of enthesitis for the patients in group I we did not identify a statistically significant difference (p=0.666>0.05).

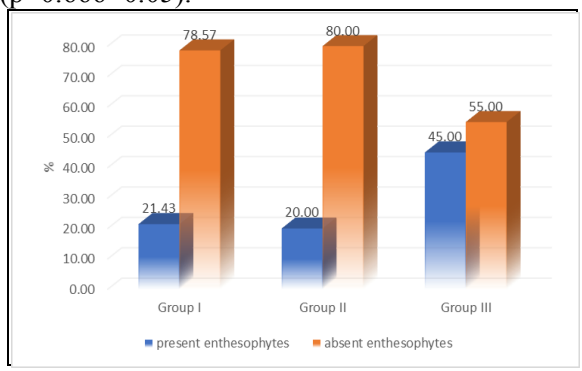

Figure 7. Group distribution regarding enthesophyte presence.

The presence of enthesophytes showed significant differences between the three groups, the patients in groups I and II being affected only in proportion of 21.43% and 20% respectively, less than the patients in group III+45% (p=0.027<0.05).

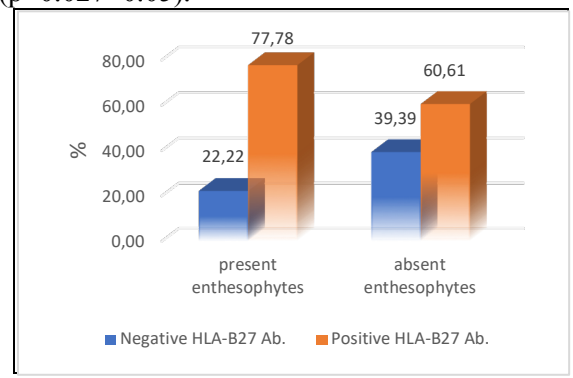

Figure 8. Relationship between enthesophytes and HLA-B27.

For patients in group I, we did not identify any significant relationship between the presence of HLA-B27 antigen and enthesophytes (p=0.341>0.05).

Sacroiliitis is one of the positive diagnostic criteria for ReA, but also a common characteristic of the seronegative SpA group.

Radiological changes in the lumbar spine may be: symmetrical syndesmophytes (vertical tract with bridge formation), asymmetrical coarse syndesmophytes, osteophytes (horizontal trajectory).

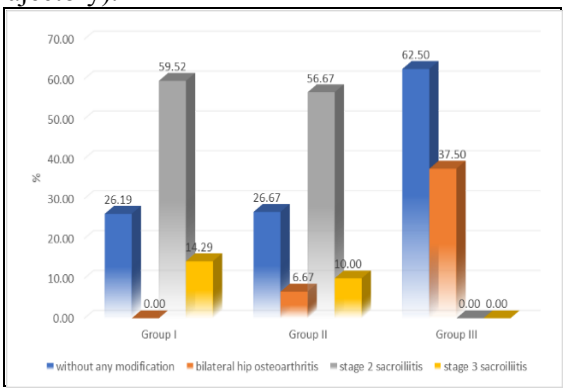

Figure 9. Group distribution regarding pelvic X-ray.

Analyzing the pathological aspects identified on pelvic X-ray we identified significant differences between the three groups (p<0.001), the patients in group III having no sacroiliitis, unlike patients in group I (74.81%) and II (66.67%) who had sacroiliitis.

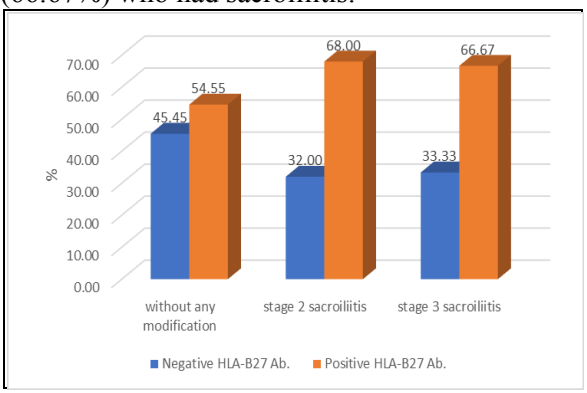

Figure 10. Relationship between HLA-B27 and X-ray.

We did not notice significant differences between patients with HLA-B27 positive or negative, respectively, with regard to the pathological aspects identified on the pelvic X-ray (p=0.734>0.05).

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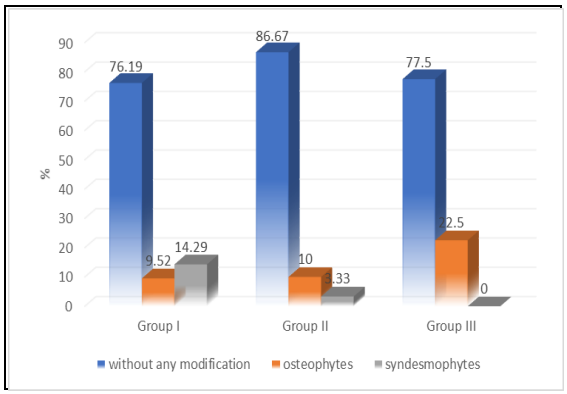

Figure 11. Group distribution regarding lumbar spine X-ray.

Analyzing the pathological aspects identified on the lumbar spine X-ray we identified significant differences between the three groups ($p<0.05$), the patients in group III exhibiting significantly higher osteophytes (22.50% vs.9.52% and 10%, respectively).

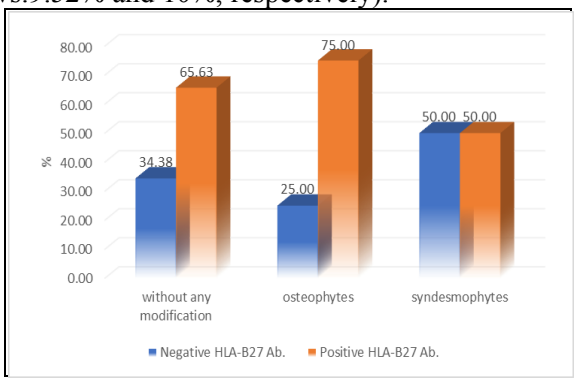

Figure 12. Relationship between HLA-B27 and lumbar spine X-ray.

We did not notice significant differences between patients with HLA-B27 positive or negative, respectively, in terms of pathological aspects identified on the lumbar X-ray ($p=0.684>0.05$).

Discussion

Seronegative SpA is a group of inflammatory joint diseases that differentiates from a genetic and clinical point of view towards rheumatoid arthritis [7].

These include the following conditions: ankylosing spondylitis, reactive arthritis, psoriatic arthritis, enteropathic arthritis, non-radio figure ic spondyloarthritis. ReA is an inflammatory joint disease, which occurs at about 1-4 weeks from a genitourinary or digestive infection, most commonly in HLA-B27 positive patients [8,9].

From a clinical point of view, most frequently the disorder starts peripherally, affecting the knees and ankles asymmetrically. It is important to know that not only joints, but also periarticular components such as tendons, muscle fascicles or ligaments are also affected. Often an indicator of the presence of this disease is the emergence of talalgia that can emphasize the presence of an enthesitis in the Achilles tendon or plantar fasciitis. A major feature of the SpA group is the presence of sacroiliitis.

HLA-B27 defines the genetic character of this group, being identified in the ReA in a proportion of 64.29%. Its presence is associated with a more severe arthritis development, frequent extraarticular manifestations and an unfavorable prognosis [10].

ELISA and PCR techniques were used to determine the antigen [11,12,13].

As noted above, identifying this antigen in ReA can partially explain the frequency of extraarticular manifestations [14,15].

The diagnosis of the disease is considered unfavorable, because ReA can evolve towards ankylosing spondylitis especially in the absence of adequate or late treatment.

Talalgia is another way of ReA onset, due to the Achilles enthesitis or plantar fasciitis. The most frequent enthesitis encountered in the group of seronegative SpA are: the Achilles tendon, patellar and quadricipital tendon.

In group I, where the frequency was higher, both Achilles and patellar enthesitis were evaluated, with the first category being most often identified.

Although the relationship between the presence of the antigen and enthesitis in patients in the first group was not statistically significant, still 20 (62.5%) HLA-B27 positive patients had enthesitis compared to 12 (37.5%) HLA-B27 negative.

So, in those with the genetic marker, the number of patients with enthesitis almost doubled highlighting a possible correlation between the antigen and these imaging changes. We can say the same thing about erosions.

Unlike enthesitis, erosions also occurred in group III (37.5%), but if we refer to the first two groups, we will notice a significant relationship regarding HLA-B27. More specifically, in HLA-B27 positive patients (68.97%), erosions were found to be twice as numerous.

Erosions can be identified in various diseases, whether inflammatory or degenerative, therefore it is very important to investigate carefully and to pay attention not only to the aspect, location or

size, but also to the anamnesis and especially the objective exam that can guide us from the beginning to a certain type of disorder.

Enthesophytes are characteristic of arthritic disease, being mostly found in the third group (45%) and in a smaller percentage in the second group (20%).

Sacroiliitis is a radiological change characteristic to the seronegative SpA group, being the result of an inflammatory condition and osteitis of the subchondral bone [16].

They are graded in five stages, the most commonly encountered during the onset of ReA being the asymmetrical stage 2.

Stage 2 sacroiliitis involves the presence of blurred bone contours, subchondral bone resorption, pseudo-enlargement and discrete sclerosis.

In group I 68% of the stage 2 sacroiliitis was identified in HLA-B27 positive patients and 32% in HLA-B27 negative, which shows another connection between the antigen with both joint destruction and a possible unfavorable evolution of ReA.

On the other hand, sacroiliitis was also found in patients from group II (66.67%) in a rather high proportion, taking into account the disorder belonging to the group of seronegative SpA.

Conclusions

HLA-B27 is linked to a severe arthritis development, more specifically to the appearance of sacroiliitis, but also to enthesitis.

This particular antigen specific to the group of seronegative spondylarthritis determines the acceleration of articular destruction, translated by erosion, and the evolution of sacroiliitis to a more advanced stage.

HLA-B27 may suggest a possible evolution of a reactive arthritis towards ankylosing spondylitis.

Conflict of interests

None to declare.

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