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HLA-B27 status and its association with clinical, laboratory and imaging features in reactive arthritis: A cross-sectional study

Status HLA-B27 i njegova povezanost s kliničkim, laboratorijskim i slikovnim značajkama kod reaktivnog artritisa: presječna studija

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Descriptors
ARTHRITIS, REACTIVE – diagnosis, immunology, microbiology;
HLA-B27 ANTIGEN – analysis, genetics, immunology;
BACTERIAL INFECTIONS – complications, microbiology;
URINARY TRACT INFECTIONS – complications, microbiology;
SACROILIITIS – diagnostic imaging

SUMMARY. *Background:* Reactive arthritis (ReA) is an inflammatory rheumatic disease that belongs to the group of spondyloarthritis (SpA). Etiopathogenesis of ReA, as well as the majority of other SpA entities, is linked with the presence of HLA-B27. However, considerable uncertainty remains regarding the HLA-B27 positivity and its association with the source of infection, clinical, laboratory, and imaging features in ReA. *Aim:* To assess the prevalence of the HLA-B27 antigen and its relationship with gender and age at onset, source of infection, features of peripheral arthritis, presence of sacroiliitis, and inflammatory burden of ReA. *Methods:* Patients diagnosed with ReA, who were hospitalized for a work-up and treatment, were evaluated for HLA-B27 status. Demographic data (gender and age at onset), ESR and CRP, number and distribution of clinically affected joints, and presence of sacroiliitis imaging on MRI were obtained and analyzed towards HLA-B27 positivity. Statistical significance was set at $P<0.05$. *Results:* A total of 224 patients with a mean age of 32.2±6.9 years were included. The majority were males (135 patients, 60.3%) ($P = 0.0021$), and the disease mostly started in the age group of 30–39 years ($P<0.00001$). The overall prevalence of HLA-B27 was 70.5%, with no significant association with any gender ($P=0.153$). C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels were significantly higher in HLA-B27 positive patients (for both $P =0.001$). There was a tendency to observe sacroiliitis more frequently in HLA-B27 positive patients, although the result did not reach significance ($P = 0.0517$). Compared to other locations urogenital tract infection was associated with the highest prevalence of HLA-B27 positivity ($P<0.00001$). *Conclusion:* In our study of ReA patients, results indicate that profiling based on HLA-B27 status can be associated with a urogenital source of infection and is valuable for predicting a higher level of systemic inflammation, as well as a tendency to detect sacroiliitis.

Deskriptori
REAKTIVNI ARTRITIS – dijagnoza, imunologija, mikrobiologija;
HLA-B27 ANTIGEN – analiza, genetika, imunologija;
BAKTERIJSKE INFEKCIJE – komlikacije, mikrobiologija;
INFEKCIJE MOKRAĆNOG SUSTAVA – komplikacije, mikrobiologija;
SAKROILEITIS – slikovna dijagnostika

SAŽETAK. *Pozadina:* Reaktivni artritis (ReA) je upalna reumatska bolest koja pripada skupini spondiloartritisa (SpA). Etiopatogeneza ReA, kao i većine drugih entiteta SpA, povezana je s prisutnošću HLA-B27. Međutim, ostaje znatna neizvjesnost u pogledu pozitivnosti HLA-B27 i njegove povezanosti s izvorom infekcije, kliničkim, laboratorijskim i slikovnim značajkama u ReA. *Cilj:* Procijeniti prevalenciju antigena HLA-B27 i njegovu povezanost sa spolom i dobi na početku, izvorom infekcije, značajkama perifernog artritisa, prisutnošću sakroileitisa i upalnim opterećenjem ReA. *Metode:* Pacijentima s dijagnozom ReA, koji su bili hospitalizirani radi pregleda i liječenja, procijenjen je HLA-B27 status. Demografski podatci (spol i dob na početku), SE i CRP, broj i distribucija klinički zahvaćenih zglobova te prisutnost slike sakroileitisa na MR dobiveni su i analizirani prema HLA-B27 pozitivnosti. Statistička značajnost postavljena je na $P < 0,05$. *Rezultati:* Uključena su ukupno 224 bolesnika prosječne dobi 32,2 ± 6,9 godina. Većina su bili muškarci (135 bolesnika, 60,3%) ($P = 0,0021$), a bolest je uglavnom počela u dobnoj skupini od 30 do 39 godina ($P < 0,00001$). Ukupna prevalencija HLA-B27 bila je 70,5%, bez značajne povezanosti s bilo kojim spolom ($P = 0,153$). Razina C-reaktivnog proteina (CRP) i sedimentacije eritrocita (SE) bila je značajno viša u HLA-B27-pozitivnih bolesnika (za oboje $P = 0,001$). Postojala je tendencija češćeg opažanja sakroileitisa u HLA-B27-pozitivnih pacijenata, iako rezultat nije dosegao značajnost ($P = 0,0517$). U usporedbi s drugim lokacijama, infekcija urogenitalnog trakta bila je povezana s najvećom prevalencijom HLA-B27 pozitivnosti ($P < 0,00001$). *Zaključak:* U našoj studiji pacijenata s ReA, rezultati pokazuju da profiliranje temeljeno na statusu HLA-B27 može biti povezano s urogenitalnim izvorom infekcije i dragocjeno je za predviđanje više razine sistemske upale, kao i tendencije otkrivanja sakroileitisa.

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Reactive arthritis (ReA) is a non-suppurative inflammatory joint disease that falls into spondyloarthritis, a group of inflammatory arthritis diseases that share common etiopathogenetic, clinical, and imaging features.[1] The disease is characterized by peripheral manifestations (e.g.,arthritis and enthesitis), axial disease (e.g.,sacroiliitis), as well as mucocutaneous and ocular manifestations. ReA occurs two to four weeks, but sometimes even six months following an infection that triggers the immunological process, eventually leading to symptoms and signs of the disease.[2] Most often, it is an infection of urogenital (UG) or gastrointestinal (GI) origin, although there is evidence of its association with nasopharyngeal and respiratory infections, too.[3]

Mostly detected culprit bacteria associated with ReA are *Chlamydia, Ureaplasma, Salmonella, Shigella, Neisseria, Staphylococcus*, and *Streptococcus*, although a wide range of infectious agents and even certain medications have been identified to incite ReA.[4–7]

Although the exact pathophysiological mechanisms remain unclear, it is established that following bacterial infection the immune response involves HLA-B27, a class I surface antigen that presents bacterial peptides to $CD8^+$ T lymphocytes, thereby initiating an autoimmune inflammatory process affecting joints and extra-articular tissues. Molecular mimicry, where HLA B-27 presents arthritogenic bacterial peptides to T cells, stimulating an autoimmune response, is considered a key pathogenic mechanism in ReA. Another hypothesis is that HLA-B27 may act as an autoantigen, i.e., the target of the immune system.[8]

Genetic predisposition, alongside male sex are considered to have a significant role in the incidence and prevalence of the disease.[9] Approximately 100 HLA-B27 subtypes have been identified, of which HLA-B2702, HLA-B2704, and HLA-B*2705 are most strongly associated with spondyloarthritis, including ReA.[10] Although certain HLA-B27 subtypes exert protective effects, the majority contribute to disease susceptibility.[11]

Heterogeneity of clinical manifestations presents a challenge in making a diagnosis of ReA.[3] HLA-B27 represents a predisposing rather than a deterministic factor.[12] Not all ReA patients are HLA-B27 positive, nor do all HLA-B27 positive individuals develop the disease. Nevertheless, its role is sufficiently important that ReA is often classified based on HLA-B27 status.[13] So, characterization of the various aspects of the disease, including the HLA-B27 status, might help in timely identifying and appropriately treating these patients.

The aim of this study was to assess the prevalence of HLA-B27 in patients with ReA and its association with gender and age at onset, source of infection, number of affected peripheral joints, presence of sacroiliitis, and inflammatory burden of the disease.

Material and methods

This was a cross-sectional study that enrolled patients with an established diagnosis of ReA, who were hospitalized for work-up and treatment from December 2020 to December 2025, at the Rheumatology Clinic – University Clinical Centre of Kosova, Clinic for Rheumatic Diseases in Prishtina (Kosova).

The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Medical Ethics Committee of the University Clinical Centre of Kosova (approval number: 183/2020; Issue date: 01/12/2020), valid for all co-authors involved in the treatment and evaluation of patients in this study. Prior to their inclusion in the study, all participants signed informed consent. The identity of patients was never disclosed.

The diagnosis of ReA was established according to the criteria issued during the fourth International Workshop on Reactive Arthritis, Berlin, Germany, where a list of general guidelines concerning the classification and diagnosis of ReA was issued.[14] There are major and minor criteria. Major criteria include: 1. Arthritis, meeting two of the following three characteristics: asymmetric, mono- or oligoarthritis, and lower limb involvement; 2. Preceding symptomatic infection, meeting one of the following characteristics: enteritis, defined as at least one day of diarrhea occurring three days to six weeks before the onset of arthritis, or urethritis, defined as dysuria or discharge for at least one day occurring three days to six weeks before the onset of arthritis. Minor criteria are: presence of a triggering infection, as evidenced by positive urine culture, cervical/urethral swab, or stool culture, and presence of persistent synovial infection, as evidenced by positive immunohistology or PCR. Patients with a definite diagnosis of ReA must have both major criteria and at least one minor criterion. Patients with a probable diagnosis of ReA must have both major criteria or one major and one minor criterion. In our study, we used the criteria of definitive diagnosis.

For all participants, data from their medical records were obtained during hospitalization (2–4 week duration), and entered into an electronic data sheet. The obtained data consisted of five domains: demographics, clinical symptoms of peripheral arthritis, laboratory, microbiology analysis, and imaging. Demographic data included gender (male/female) and age at onset (years). Signs of arthritis included swollen joint count, examined clinically on 66 joint count system.[15] Laboratory data included C-reactive protein (CRP) measured by ELISA (mg/L), and erythrocyte sedimentation rate (ESR) measured by the standard Wester-

gren method (per hour). As for identification of the HLA-B27 antigen, after isolation of DNA from 200 ml of whole blood by RT PCR method with specific primers that mark a conserved region of HLA-B27, while the β-globin gene is included in the internal control reaction. The results are visualized using Taqman probe (CE/IVD kit). Regardless of the possible previous symptoms of infection, all the patients had a urine culture, cervical/urethral swab, as well as nasopharyngeal swab, and stool culture, analysed for a standard set of bacteria. The isolation of microbial pathogens was carried out at the Institute of Microbiology and included: *Salmonella spp., Shigella spp., Campylobacter jejuni, Yersinia* and *Clostridium difficile* with feces, *Ureaplasma urealyticum* with culture, *Neisseria gonorrhea* with urethral smear, *Enterococcus* and *Escherichia coli* with urine, *Chlamydia trachomatis* and *Treponema pallidum* with IgG and IgM serological tests, *Mycoplasma genitalium* with urethral smear, *Streptococcus B haemolyticum* of gr A and B with throat smear, and *Mycobacterium tuberculosis* with TB gold test. All the laboratory and microbiology processes were performed in accordance with the ISO/IEC 17025 standard, including quality control tests. Imaging consisted of magnetic resonance imaging (MRI) of the sacroiliac joint, which was performed at the Institute of Radiology with MRI devices of the Siemens Healthcare – Magnetom, GE HealthCare – Signa, and Philips Healthcare – BlueSeal type. Sacroiliitis was defined according to the ASAS criteria, with bone marrow edema (BE) or osteitis of the sacroiliac joints, on a T2-weighted sequence sensitive for free water (such as short tau inversion recovery (STIR) or T2FS) or bone marrow contrast enhancement on a T1-weighted sequence (such as T1FS post-Gd), with inflammation that must be clearly present and located in a typical anatomical area (subchondral bone), and that the MRI appearance must be highly suggestive of a spondyloarthritis.[16]

Statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were presented as frequencies and percentages. Before further testing, normality of continuous variables was assessed using the Kolmogorov-Smirnov test. They were summarized as means ±SD. If normally distributed the difference between groups was tested using Student's t-test. For categorical variables, differences in frequencies between groups were tested with the χ^2 (Chi) test at the 95% $p<0.05$ and 99.7% $p<0.001$ confidence levels. A P-value less than or equal to 0.05 was considered statistically significant.

Results

Overall, 224 patients with an established diagnosis of ReA were enrolled in the study. Among them, 158 patients (70.5%) were HLA-B27 positive.

Table 1. Distribution of patients according to age groups
Tablica 1. Raspodjela bolesnika prema dobnim skupinama

Age groups (in years) / Dobne skupine (u god)	N	%	X^2; df; P-Value
<20	12	5.4	X^2=113.107; df=3; P=0.00001 –
20–29	61	27.2	
30–39	118	52.7	
40–49	31	13.8	
50≥	2	0,9	
Total / Ukupno	224	100.9	

Of the total number of patients, 135 (60.3%) were males, and 89 (39.7%) were females. There was a statistically significant difference in distribution by gender (X^2=9.446; DF=1; P=0.0021), indicating that males were significantly more frequently represented in this disease. The mean age of the patients was 32.26.9 years, indicating a relatively young population. There was a significant difference in the distribution of patients by age groups (P<0.00001), indicating that the age group 30–39 years constitutes the dominant group in the studied population (Table 1).

Statistical analysis revealed no significant difference in the distribution of HLA-B27 by gender (P=0.153) (Table 2).

The number of clinically affected joints ranged from one to four, and their distribution according to gender and in total is presented in Table 3.

Results showed that the number of arthritis joints differed significantly between men and women. Women tend to present with involvement of more joints (3–4 joints), while men more often present with monoarthritis or involvement of a smaller number of joints, but there was no statistically significant difference.

As for the association of HLA-B27 status and the number of swollen joints, no association was found (Table 4).

Patients with positive HLA-B27 had significantly higher levels of CRP and ESR in comparison to HLA-B27 negative patients (for both P=0.001), which is presented in Table 5.

Out of 224 patients, 57 (25.4%) had sacroiliitis on MRI. The presence of sacroiliitis on MRI was analyzed against HLA-B27 status (Table 6). Of the patients with inflammation of the sacroiliac joint, most (46; 80.7%) were HLA-B27 positive. On the other hand, out of 167 patients with no sacroiliitis, 112 (67.1%) were HLA-B27 positive, while 55 (32.9%) were HLA-B27 negative. The result showed a tendency towards an association between HLA-B27 status and the presence of sacroiliitis, but the result did not reach the level of significance (P=0.0517).

Table 2. Distribution of HLA-B27 status according to gender
Tablica 2. Raspodjela HLA-B27 statusa prema spolu

HLA-B27			Positive / Pozitivan	Negative / Negativan	Total / Ukupno	X^2; df; P-value
Gender / Spol	Males / Muškarci	N	100	35	135	X^2=2.037; df=1; P=0.153
		%	74.1	25.9	100.0	
	Females / Žene	N	58	31	89	
		%	65.2	34.8	100.0	

Table 3. Distribution of swollen joint count according to gender
Tablica 3. Raspodjela broja otečenih zglobova prema spolu

Swollen joint count / Broj otečenih zglobova	Gender / Spol				Total / Ukupno		χ^2; df; p; Cramer's V
	Males / Muškarci		Females / Žene				
	N	%	N	%	N	%	
1	57	42.2	22	24.7	79	35.3	χ^2 = 9.563; df = 3; p = 0.023; Cramer's V = 0.207
2	52	38.5	39	43.8	91	40.6	
3	21	15.6	19	21.3	40	17.9	
4	5	3.7	9	10.1	14	6.3	
Total / Ukupno	135	100.0	89	100.0	224	100.0	

Table 4. Distribution of swollen joint count according to HLA-B27 status
Tablica 4. Raspodjela broja otečenih zglobova u odnosu na HLA-B27 status

Swollen joint count / Broj otečenih zglobova	HLA B 27			Chi-square value; df; P-value
	Positive / Pozitivan	Negative / Negativan	Total / Ukupno	
	N (%)	N (%)	N (%)	
1	63 (79.7)	16 (20.3)	79 (100.0)	Chi-square = 6.75; df = 3; P-value = 0.08
2	62 (68.1)	29 (31.9)	91 (100.0)	
3	23 (57.5)	17 (42.5)	40 (100.0)	
4	10 (71.4)	4 (28.5)	14 (100.0)	
Total patients / Ukupno bolesnika (N)	158 (70.5)	66 (29.5)	224 (100.0)	

Table 5. Laboratory parameters of systemic inflammation according to the HLA-B27 status
Tablica 5. Laboratorijski parametri sistemske upale u odnosu na status HLA-B27

Laboratory parameters / Laboratorijski parametri	HLA B 27		Welch's t-test; df; p-value
	Negative / Negativan	Positive / Pozitivan	
ESR/1h / SE/1h – Mean ± SD / Srednja vrijednost ± SD	34.2 ± 6.6	50.2± 10.0	Welch t test =13.7;df = 189.1; P < 0.001
CRP mg/L – Mean±SD / Srednja vrijednost ± SD	27.3± 6.5	45.3± 10.4	Welch t test =17.4;df = 194.2; P < 0.001
Total patients / Ukupno bolesnika (N)	66	158	–

Among locations of identified sources of infection, the most prevalent were those arising from the urogenital tract (Table 7). These infections were more frequently associated with HLA-B27 positivity (89.3%), while gastrointestinal and nasopharyngeal/respiratory infections had a more balanced distribution between the positive and negative HLA-B27 antigen, also with a lower prevalence of HLA-B27 positivity compared to urogenital tract infections. These results showed that the prevalence of HLA-B27 was significantly higher in patients with urogenital infections ($P < 0.00001$), suggesting a strong association between HLA-B27 and sources of urogenital tract infections as a trigger for ReA.

Table 6. Presence of sacroiliitis according to the HLA-B27 status
Tablica 6. Prisutnost sakroileitisa u odnosu na HLA-B27 status

Sacroiliitis / Sacroileitis	HLA-B27				Total / Ukupno		X^2; df; P-value
	Negative / Negativan		Positive / Pozitivan				
	N	%	N	%	N	%	
No / Ne	55	32.9	112	67.1	167	100	$X^2 = 3.78$; df = 1; P = 0.0517
Yes / Da	11	19.3	46	80.7	57	100	
Total / Ukupno	66	29.5	158	70.5	224	100	–

Table 7. HLA-B27 status according to the location of infection
Tablica 7 HLA-B27 status u odnosu na mjesto infekcije

Source of infection / Izvor infekcije	HLA B 27				Total / Ukupno		X^2; df; P-value
	Negative / Negativno		Positive / Pozitivno				
	N	%	N	%	N	%	
Gastroenteric infection / Gastrointestinalna infekcija	27	46.6	31	53.4	58	100.0	$X^2 = 37.82$; df = 2; P < 0.00001
Nasopharyngeal or respiratory infection / Nazofaringealna ili respiratorna infekcija	23	51.1	22	48.9	45	100.0	
Urogenital tract infection / Urogenitalne infekcije	13	11.1	104	88.9	117	100.0	
Total / Ukupno	63	28.6	157	71.4	220	100.0	–

Discussion

In our study, patients with an established diagnosis of ReA were evaluated for HLA-B27 status and its association with gender, age at onset, biomarkers of systemic inflammation, the number of swollen joints, the presence of sacroiliitis (as detected on MRI), and the location of the triggering infection. The results showed that the majority of patients were HLA-B27 positive, and there was a significant relationship between HLA-B27 positivity and higher CRP levels, sacroiliitis, and a urogenital source of infection.

Out of 224 patients with an established diagnosis of ReA who were enrolled in the study, 70.5% were HLA-B27 positive. Studies have demonstrated that the prevalence of positive HLA-B27 in ReA ranged from 50 to 80%.[2,17] Susceptibility to the development of ReA is markedly more significant in patients with positive HLA-B27 compared to the general population and may pose a risk to the development of more chronic arthritis.[12] Therefore, our results confirm the central role of this antigen in the pathogenesis of the disease and are in accordance with other studies and reviews.[18]

Regarding the distribution by gender, our results showed that males were significantly more frequently represented in this disease. It is commonly accepted that ReA is more frequent in males under 40 years old.[19,20] So, our findings are consistent with the notion that ReA is inflammatory rheumatic disease with male predominance of younger age, and is associated with a higher prevalence of urogenital infections, especially *Chlamydia trachomatis*, with a more pronounced role of HLA-B27 in men, and a more aggressive immune response to causative pathogens.[21,22]

However, there are studies showing predominance of women in ReA.[23] This might depend on the location of the triggering infection. Post-enteric infections are similar between men and women.[8] Study by Townes et al. stated that in ReA associated with enteric infection, the relative risk was higher for women than for men (RR = 1.5 vs) and in adults than for children (RR = 2.5).[24]

As for the gender distribution of HLA-B27, its positivity was more frequent in men than in women.[25] Although such data for ReA are generally scarce, some older studies showed a gender difference in the prevalence of HLA-B27 in ReA, with the gene generally being found more frequently in males, particularly in cases linked to sexually acquired infections.[26]

The gender HLA-B27 difference might explain the different presentation of axSpA in men and women, such as radiological progression.[27]

In our study, positivity of HLA-B27 was associated with a numerically higher number in men compared to women, but eventually, no significant association was found. In a much smaller study of 25 patients (19 HLA-B27 negative patients and six HLA-B27 positive

patients) with ReA, there was no difference in the number of swollen joints based on HLA-B27 positivity. [28]

A range of affected peripheral joints between one and four confirms that oligoarthritis is the dominant form of clinical presentation of ReA.[20]

We chose the swollen joint as a method for clinical assessment of peripheral arthritis. Swollen joint count is a more reliable clinical tool for assessing arthritis in comparison to tender joints. SJC represents active synovial inflammation, whereas tender joints (TJC) are more closely associated with pain and patient-reported outcomes. Also, swollen joints strongly correlate with ultrasound-detected synovitis (active, inflammatory disease) and are considered a more objective, high-validity measure of inflammatory arthritis.[29] The system of 66 examined joints allowed us to capture all the relevant joints in ReA, as it is a standardized, validated, and comprehensive assessment tool used by clinicians to measure disease activity in psoriatic arthritis (PsA) and other inflammatory conditions. [30]

Studies suggest there are some gender differences in the clinical presentation of joint involvement in ReA. Our results showed that the number of arthritis joints somewhat differed between men and women. Women tend to present with involvement of more joints (3–4 joints), while men more often present with monoarthritis or involvement of a smaller number of joints. However, this difference did not reach significance. Some studies on ReA also found no difference in the oligoarticular type of ReA (73% male versus 70% female patients), as well as in the monoarticular type (14% male versus 13% female patients).[20]

As for the level of the markers of systemic inflammation in our sample, we found levels significantly higher than the upper level of the normal range. In the acute phase of ReA, the inflammatory markers such as ESR and CRP tend to be higher.[31] However, in one study it was shown that in chlamydial ReA acute phase reactants, including ESR and CRP, were mostly within normal ranges.[32]

Significantly higher levels of CRP in patients with positive HLA-B27, compared to HLA-B27 negative patients, suggest a more pronounced pathogenetic systemic inflammatory activity in this group, which should be considered when establishing a diagnosis. There is a very small number of papers that we can correlate in that regard. The only paper that we could find is the paper by Townes et al.[33] The authors also found that patients who were HLA-B27 positive demonstrated significantly higher CRP levels compared with HLA-B27 negative patients. In addition, HLA-B27 positivity was associated with a greater overall disease activity, reflecting a more pronounced inflammatory clinical presentation.

In our sample, around 25% had sacroiliitis on MRI, and the majority were HLA-B27 positive rather than negative. From axSpA studies, it is well-known that the presence of the HLA-B27 allele is associated with a greater chance for a positive MRI of the SI joints.[34]

Although the results showed a strong tendency towards such an association, the results in our sample did not reach the level of significance. The lack of (full) statistical significance may be related to the sample size, especially the relatively small number of patients with sacroiliitis, or to the clinical heterogeneity of the study population.

There is a lack of clinical research on sacroiliac joint inflammation associated with the prevalence of HLA-B27. In the small retrospective study of HLA-B27 positive and HLA-B27 negative patients with ReA, HLA-B27 positive patients had more axial symptoms.[28] No significant difference was found regarding MRI of sacroiliac joints, with the notion that the numbers were very small, and no reliable conclusions could have been drawn. Namely, just nine out of 25 patients had MRI, among whom four were HLA-B27 positive and five HLA-B27 negative, and only two HLA-B27 negative patients showed signs of sacroiliitis. Other clinical research on this aspect was mostly studied in seronegative spondyloarthropathy, which also included ReA or psoriatic arthritis.[18,35–37] Our findings are important because they show that patients with ReA who are HLA-B27 positive might have a higher probability of developing sacroiliitis detected on MRI, even in the early stages of the disease.

The distribution of HLA-B27 varies significantly according to the source of infection and the type of bacteria, indicating the influence of genetic-immunological interactions on the specific pathogen. The risk of developing ReA after infection is different depending on the source of the infection.[1]

When evaluating the association of the location of triggering infection and HLA-B27 status, our results suggest a strong pathogenetic link between urogenital infections and HLA-B27, especially in comparison to also very prevalent gastrointestinal infections.

The paper by Tiovonen A. and Toivonen P. highlighted pathogenetic differences between post-enteric and urogenital ReA, with a higher prevalence of HLA-B27 in the latter.[38] Immunogenetic studies have demonstrated that HLA-B27 favors the intracellular persistence of urogenital pathogens, inducing a prolonged and often chronic inflammatory response.[8]

In contrast, patients with gastrointestinal infections (e.g., *Salmonella, Shigella, Yersinia, Campylobacter*) show a lower prevalence of HLA-B27 positivity, suggesting that post-enteric ReA may develop more frequently even in HLA-B27 negative individuals, perhaps through immune mechanisms independent of

this antigen. Meanwhile, the almost equal prevalence of HLA-B27 positivity and negativity in respiratory/nasopharyngeal infections suggests that these infections have a more limited or indirect role in the classic pathogenesis of ReA and may represent atypical forms or differential diagnoses. However, this might be influenced by the arthritic pathogen. One study found that the correlation between HLA-B27 positivity is higher in Shigella-induced ReA than in other enteropathic infections.[12]

Susceptibility to the development of ReA is markedly more significant in patients with positive HLA-B27 compared to the general population and may pose a risk to the development of more chronic arthritis. In the study spanning 30 years Brinster et al. analyzed clinical, biological, and imaging characteristics as well as therapeutic management comparing two periods of sixty-two patients. Regarding the predictive factors of worse prognosis of ReA, HLA-B27 positivity, Chlamydia-induced infection, spondyloarthropathy family history, and chronic bowel inflammation were the factors that contributed the most to the severity and progression of the disease.[39]

The strength of our study is the large number of patients with an established diagnosis of ReA and a systematic approach and analysis of key characteristics of ReA.

Limitations of this study include the absence of information regarding other symptoms than those musculoskeletal (including mucocutaneous and eye symptoms), lack of data regarding the time between symptoms of previous infections and symptoms of ReA, including arthritis. Our work was aimed to evaluate the most prominent rheumatological features that might be associated with HLA-B27 positivity in ReA. According to our main objective, we have not analyzed other HLA antigens. For identifying arthritis, we used clinical examination, not a more sophisticated method such as ultrasound, and we did not obtain data on enthesitis or dactylitis, which might be found in ReA, too. Although we identified the genitourinary tract as the predominant localization of triggering infections, for this work, we did not show data on specific bacteria that were found, as we plan to publish it in a separate article focusing mostly on microbiology issues. In recent years, there have been more data that the gut microbiome might have implications in the pathogenesis of arthritis, including SpA.[2] We had no opportunity to tackle this subject.

Overall, the results of our study support the concept that HLA-B27 is not only a predisposing genetic factor, but also closely interacts with the type of inciting infection, influencing the clinical expression and the risk for more severe or chronic forms of the disease. Therefore, identification of the source of infection and HLA-B27 status has important diagnostic, prognostic and therapeutic value in the management of patients with ReA.

The study contributes to a better understanding of ReA. It displays the similarities and differences in clinical manifestation, imaging features, and laboratory inspection between HLA-B27 negative patients and HLA-B27 positive patients. The results prove that ReA patients with different genetic backgrounds show various manifestations, although they encounter similar infections.

Conclusion

In our large study of patients with an established diagnosis of ReA, we showed that HLA-B27 plays a central role in the clinical expression and immunopathogenesis of the disease. HLA-B27 positive patients exhibited higher systemic inflammatory activity. ReA predominantly affected young males and was more frequently associated with urogenital infections, which also showed a strong association with HLA-B27 positivity. Some other tendencies of more affected joints in women than in men, and the association between HLA-B27 positivity and the presence of sacroiliitis on MRI did not reach the level of significance. Altogether, HLA-B27 status together with the causative infection is essential for risk stratification, prognosis prediction, and clinical management of patients with ReA. Early identification of HLA-B27 positive patients, especially those with urogenital infections, may help in early evaluation with MRI, closer follow-up, and individualized treatment to prevent progression to axial spondyloarthritis. New studies with a detailed approach and prospective design will elucidate mostly poorly studied ReA, as an entity within the spectrum of SpA.

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Abbreviations:

AS	– Ankylosing Spondylitis
ASAS	– Assessment of SpondyloArthritis International Society
CBC	– Complete Blood Count
CRP	– C Reactive Protein
EULAR	– European Alliance of Associations for Rheumatology
ESR	– Erythrocyte Sedimentation Rate
FC	– Flow Cytometry
HLA	– Human Leukocyte Antigen

ISO/IEC – International Organization for Standardization/International Electrotechnical Commission
MRI – Magnetic Resonance Imaging
PCR – Polymerase Chain Reaction
PCR-SSP – Polymerase Chain Reaction – Sequence-Specific Primers
ReA – Reactive Arthritis
SpA – Seronegative Spondyloarthropathies
SPSS – Statistical Package for the Social Sciences

CONFLICT OF INTEREST INFORMATION

The authors declared no conflict of interest relevant to this work.

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AUTHOR CONTRIBUTIONS

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Drafting the first version of the manuscript: AB
Critical revision of the manuscript: AB, IHB, SG

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