Medicine

HLA-B27 negative reactive arthritis versus HLA-B27 positive reactive arthritis
A retrospective study

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Abstract

Reactive arthritis (ReA) is defined as inflammatory arthritis secondary to an extra-articular infection with a key genetic background, HLA-B27. However, to date, the diagnosis and classification remain incomplete. The study focused on the similarities and differences in clinical manifestation, imaging features, and laboratory inspection between HLA-B27 negative patients and HLA-B27 positive patients in order to provide a reference for future development of diagnostic and classification criteria. Twenty-five ReA (19 HLA-B27 negative patients and 6 HLA-B27 positive patients) were included in this retrospective study. Clinical data, including demographics, clinical symptoms, imaging features, and laboratory inspection, were collected. The chi-square test and Mann–Whitney U test were used in the analysis. HLA-B27 negative group showed more involvement of upper extremities and small joints, while HLA-B27 positive group performed more axial symptoms. No significant difference was found in imaging features (ultrasound and magnetic resonance imaging) or laboratory inspection (microbes culture and infection-related indicators) between the 2 groups. ReA patients with different genetic backgrounds show various manifestations, although they encounter similar infections.

Abbreviations: CRP = C reactive protein, ESR = erythrocyte sedimentation rate, ReA = reactive arthritis.

Keywords: HLA-B27, infection-related arthritis, reactive arthritis, spondyloarthritis

1. Introduction

Reactive arthritis (ReA), first described by Fiessinger and Leroy in France and Dr Hans Reiter in Germany in 1916, was longly named by Reiter syndrome. Until 1969, the term ReA was mentioned by a Finish team to define transient non-purulent arthritis.[1] However, strict sterility was questioned in later researches since several kinds of microbes were identified by PCR.[2,3] Although no perfect diagnostic criteria have been developed until now, 2 key points are requisite, including preceding infection and typical arthritis. A preceding enteric or genitourinary infection is considered to be a trigger in most criteria since *Chlamydia trachomatis*, Enterobacteriae and *Campylobacter* were discovered in ReA most frequently.[4,5] The typical arthritis often performs as monoarthritis or oligoarthritis, usually affecting the lower extremities.[6] Currently, ReA is identified as a subtype of spondyloarthritis because of its symptoms and the association with HLA-B27. Reports showed that the prevalence of ReA in B27-positive individuals is 5 to 10 times greater than in the general population.[7] Different hypotheses like HLA-B27 misfolding hypothesis have been raised to explain the role of HLA-B27, but the exact pathogenesis remains unclear.[8]

In clinical practice, we noticed that a group of patients with negative HLA-B27 also developed ReA after a urinary or intestinal infection. Differed from the typical asymmetric monoarthritis or oligoarthritis affecting lower limb, some of these patients presented symmetrical arthritis involving more than 5 joints. Though these patients could not be diagnosed as ReA under strict criteria, there was no more proper diagnosis after careful screening. The study aimed to explore the clinical features of HLA-B27 negative ReA and the difference between HLA-B27 negative and HLA-B27 positive ReA in order to afford more information for the development of the definition and diagnostic criteria.

2. Methods

2.1. Patients

This study was designed single-center and retrospective. All patients diagnosed with ReA from the rheumatology department of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine with a complete medical history including symptoms and blood examination from February 2014 to December

2021 were included. Diagnostic criteria were based on the third international workshop on ReA,[6] which consisted of 3 items: Typical peripheral arthritis (asymmetric monoarthritis or oligoarthritis usually of the lower extremities); Evidence of preceding infection; Exclusion of other known causes of mono/oligoarthritis. Moreover, patients with preceding diarrhea or urethritis but did not perform critically typical arthritis were included if there was no more appropriate diagnosis currently. Exclusion criteria were: Other kinds of infection with post-infectious arthritis. Can be diagnosed as septic arthritis, spondyloarthritis, disseminated gonococcal infection, enteroviral infection, Whipple disease, inflammatory bowel disease, Behcet disease, crystalline arthropathy, Lyme disease, post-streptococcal arthritis. This study was approved by the ethics board of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine.

2.2. Clinical and laboratory data

The data was composed of 4 parts, which included demographics, clinical symptoms, laboratory inspection, and imaging features. Demographics included gender, age, and family or personal history of spondyloarthritis, psoriasis, and inflammatory bowel disease. Clinical symptoms included the number and location of painful and swollen joints, the previous urinary and gastrointestinal symptoms, the fever, and extra-articular manifestation. Laboratory inspection included microbes culture, bacterial counts in urine, white blood cell counts in urine and blood, lymphocyte counts, C reactive protein (CRP), and erythrocyte sedimentation rate (ESR). Imaging features included ultrasound inspection and magnetic resonance imaging. Missing data in demographics, clinical symptoms, and laboratory inspection were filled by multiple imputation and regression imputation. Missing data in imaging features were reported but not counted in statistical analysis.

2.3. Statistical analysis

Quantitative variables were presented as mean ± standard deviation, and qualitative variables were described as ratios or percentages. Data were analyzed by chi-square test or Fisher exact test for qualitative data and Mann–Whitney U test for quantitative data. $P ≤ .05$ was considered significant.

3. Results

3.1. Patients' characteristics

Twenty-five patients were included, among which were 6 HLA-B27 positive and 19 HLA-B27 negative. The average age of HLA-B27 positive group was younger than HLA-B27 negative group but had no significance ($P = .253$). In HLA-B27 negative patients, 4 out of 19 (21%) were male, and in HLA-B27 positive patients there were 4 out of 6 (67%). However, the result could not be considered significant ($P = .059$). Among all patients, only one HLA-B27 positive patient declared a family history of spondyloarthritis. Table 1 shows more details.

3.2. Clinical features

HLA-B27 negative patients and HLA-B27 positive patients showed significant differences in clinical manifestation. Small joints are more likely to be involved in the negative group ($P = .05$), while the possibility of axial involvement is higher in positive group ($P = .02$). The wrist was more often involved in negative group, but the significance was uncertain ($P = .06$).

In the study, half of the patients (52% of all) did not experience any urogenital or gastrointestinal symptoms both in positive and negative group. The most commonly affected joint was the knee (72% of all), and next was the ankle (52% of all), which supported that typical ReA primarily involved the lower extremities. However, HLA-B27 negative group showed upper extremities were also affected. Most were the wrist (47% of negative group) and small joints (53% of negative group) of hands like metacarpophalangeal joints, which was not observed in positive group. Axial symptoms such as back pain and hip pain were frequently observed in positive group (83% in positive group) but relatively rare in negative group (27% of negative group).

Six patients performed extra-articular manifestation, among which 5 cases were oral ulcers (3 HLA-B27 positive cases and 2 HLA-B27 negative cases), and 1 HLA-B27 negative case showed erythema nodosum. 47% of HLA-B27 negative patients had a fever, while fever did not emerge in HLA-B27 positive group. More information is described in Table 2.

3.3. Laboratory inspection

In the study, only 8 patients had positive microbe culture results, of which 6 were *Escherichia coli*. Beyond that, *Enterococcus faecium* and *Ureaplasma urealyticum* were also observed. Bacteria counts in urine were above the normal range in 37% of HLA-B27 negative patients and 17% of HLA-B27 positive patients, while white blood cell counts were higher than normal in 63% of negative group and 83% of positive group. The differences in ESR and CRP between the 2 groups were all indistinctive, which indicated that the severity of inflammation was similar. Moreover, the average of white blood cell and lymphocyte

Table 1

Patients' characteristics.

Characteristics	HLA-B27 negative (n = 19)	HLA-B27 positive (n = 6)	*P* value
Age (yr)	60.84 ± 3.48	53.83 ± 4.88	.25
Gender (male/female)	4/15	4/2	.06
Related medical history* (yes/no)	0/19	1/5	.24

*Related medical history included family or personal history of spondyloarthritis, psoriasis, and inflammatory bowel disease.

Table 2

Clinical features.

Clinical features	HLA-B27 negative (n = 19)	HLA-B27 positive (n = 6)	*P* value
Symptomatic infection (yes/no)	9/10	3/3	1.00
Painful joints (yes/no)			
Knee	15/4	3/3	.30
Ankle	10/9	3/3	1.00
Wrist	9/10	0/6	.06
Elbow	4/15	0/6	.54
Shoulder	7/12	0/6	.14
Small joints	10/9	0/6	.05
Swelling (yes/no)	15/4	6/0	.54
Axial involvement (yes/no)	5/14	5/1	.02
Extra-articular symptoms (yes/no)	3/16	3/3	.13
Fever (yes/no)	9/10	0/6	.06

counts in peripheral blood were within normal range in both groups, while the average of ESR and CRP were above normal standard (ESR ≤ 20 mm/h and CRP ≤ 10 mg/L). The result supported that ReA was post-infectious, and the manifestation of systemic infection was infrequent. Table 3 contains more description.

3.4. Imagine examination

In the study, 19 (3 HLA-B27 positive patients and 16 HLA-B27 negative patients) out of 25 patients (76%) took ultrasound inspection. Fourteen (2 HLA-B27 positive patients and 12 HLA-B27 negative patients) out of 19 patients (74%) showed synovial thickening, and 9 (1 HLA-B27 positive patients and 8 HLA-B27 negative patients) out of 19 (47%) showed joint effusion. Magnetic resonance imaging of wrist, ankle, or knee was applied to 8 (2 HLA-B27 positive patients and 6 HLA-B27 negative patients) out of 25 patients (32%). Seven (1 HLA-B27 positive patients and 6 HLA-B27 negative patients) out of 8 (85%) showed joint effusion. Nine (4 HLA-B27 positive patients and 5 HLA-B27 negative patients) out of 25 patients with axial symptoms took an MRI of sacroiliac joint to identify the damage of sacroiliac joint, while only 2 HLA-B27 negative patients showed sacroiliitis and none of them performed bone destruction. No significant difference was observed between 2 groups.

4. Discussion

The study focused on the differences between HLA-B27 negative and HLA-B27 positive patients, which implies that ReA may present different clinical syndromes according to different genetic backgrounds. HLA-B27 is closely related to spondyloarthritis, but not to infection-related arthritis. Considering that ReA lies at the intersection of spondyloarthritis and infection-related arthritis, the difference indicates that some types of ReA resemble spondyloarthritis, but other types do not.

It is widely accepted that ReA belongs to spondyloarthritis in view of its association with HLA-B27 and clinical features, including the typical asymmetrical inflammatory oligoarthritis of the lower limbs, as well as other manifestations of spondyloarthritis such as inflammatory back pain, enthesitis, and even some extra-articular symptoms like conjunctivitis and oral ulcers.[7,9] In the study, HLA-B27 positive group performed more axial symptoms and HLA-B27 negative group showed more involvement of upper extremities and small joints, which suggested that HLA-B27 positive ReA is closer to spondyloarthritis than HLA-B27 negative ReA.

However, whether ReA is an independent subtype or an initial form of other subtypes of spondyloarthritis like ankylosing spondylitis is worth pondering. Infection not only causes ReA, but is also a trigger for ankylosing spondylitis, psoriatic arthritis, and inflammatory bowel disease arthritis. Burgos-Vargas proposed that repeated gut infection may be the main inducement for the development of ankylosing spondylitis in Mexico.[10] A cohort study in Taiwan showed that Candida infection is an independent risk factor for developing ankylosing spondylitis.[11] Considering that part of the ReA patients eventually developed ankylosing spondylitis, a certain form of ReA may be regarded as an early stage of ankylosing spondylitis. Nonetheless, very few studies have focused on identifying the certain form. So far, only HLA-B27 has been reported to be a predictive factor.

In the research, HLA-B27 negative ReA performed major involvement of upper extremities and small joints, which did not correspond to typical manifestations of spondyloarthritis. According to the suggestions of the 4th International Workshop on Reactive Arthritis, the term "reactive arthritis" could be used only if the clinical picture and the infection are associated with HLA-B27 and spondyloarthritis.[10] Therefore, some rheumatologists suggested that some kind of HLA-B27 non-associated ReA should be described as "infection-related arthritis."[12]

Nevertheless, the definition of infection-related arthritis is more ambiguous than that of ReA. Several types of infection-related arthritis caused by specific pathogens unrelated to HLA-B27 have been distinguished from ReA. Post-streptococcal ReA, Lyme, and Poncet disease are the representatives, which are reported to be caused by group A β-hemolytic *Streptococcus*, *Borrelia burgdorferi*, and *Mycobacterium tuberculosis* relatively.[13–15] Meanwhile, more infection-related arthritis cannot be classified by pathogen as the exact pathogenic microorganism cannot be found. In this study, only 8 out of 25 patients got positive culture results. Another study of triggering bacteria showed that though many detection methods like culture, enzyme immunoassay, Widal agglutination, and even PCR have been applied, the causative pathogen was identified only in 56% (29/56) of patients with ReA.[16] Therefore, a general term "reactive arthritis" is necessary to describe an inflammatory arthritis not caused by an direct infection in joints but a secondary inflammatory reaction after infection at another site in current reports.[17]

In addition, preceding gastrointestinal and urinary infections are required in those ReA that can be classified as spondyloarthritis. However, besides common urinary and intestinal pathogens (like *Salmonella*, *Yersinia*, and *C. trachomatis*), other infections and vaccination also cause ReA. For example, virus (COVID-19), parasites (*Enterobius vermicularis*), and vaccination (influenza, COVID-19, tetanus) have been reported to be a trigger of ReA.[18–22] These facts reiterate that ReA may consist of several subgroups, and not all of them behave like spondyloarthritis.

Figure 1 served as a graphical representation to display the complex relationship between ReA, spondyloarthritis and infection-related arthritis. HLA-B27 represents an important genetic
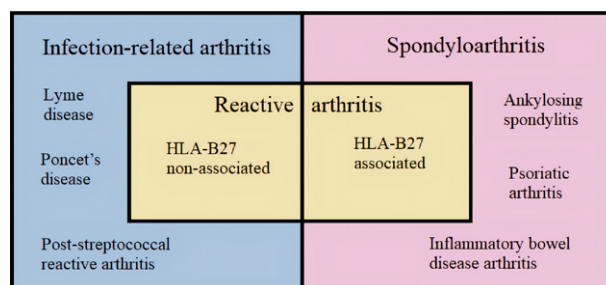
Table 3

Laboratory inspection.

Laboratory inspection	HLA-B27 negative (n = 19)	HLA-B27 positive (n = 6)	P value
Microbe culture (yes/no)	7/12	1/5	.63
Bacteria counts in urine (abnormal/normal)	6/13	1/5	.64
White blood cell counts in urine (abnormal/normal)	12/7	5/1	.63
Erythrocyte sedimentation rate (mm/h)	58.27 ± 8.26	63.20 ± 12.46	.93
C reactive protein (mg/L)	47.95 ± 12.26	37.07 ± 11.96	.39
White blood cell counts in blood (×10^9/L)	7.07 ± 0.71	7.24 ± 0.81	.67
Lymphocyte counts in blood (×10^9/L)	1.68 ± 0.22	1.94 ± 0.45	.48

Figure 1. The relationship between reactive arthritis, spondyloarthritis and infection-related arthritis.

background, while previous studies have found that HLA-B27 associated ReA is different from HLA non-associated ReA. This research showed that HLA-B27 negative group showed more involvement of upper extremities and even small joints, while HLA-B27 positive group performed more axial symptoms. The result provides new evidence for the importance of HLA-B27 in the classification of ReA, which may afford a reference for the future development of criteria.

The main limitation is the deficiency of sample capacity, but it is acceptable in consideration of the low incidence rate of ReA. The study is also limited to incomplete diagnostic criteria. The study only included patients with preceding urinary and gastrointestinal infections, so some patients with ReA secondary to other kinds of infection might have been missed.

Despite these shortcomings, 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.

Author contributions

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