

Study of clinical and laboratory profile of patients with reactive arthritis in a tertiary healthcare center



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ABSTRACT

Background: Reactive arthritis (ReA) is a spondyloarthropathic disorder characterized by joint pain and swelling triggered by an infection in another part of the body – most often the intestines, genitals, or urinary tract. This condition usually targets the knees, ankles, and feet. The present study was conducted to study the clinical, microbiological, and laboratory profile of patients with ReA and to determine the outcomes over a duration of 3 months. **Aims and Objectives:** This study aimed to assess the clinical and laboratory profile of patients with ReA in a tertiary healthcare center. **Materials and Methods:** This was a prospective analytical study undertaken in the Rheumatology Out Patient Department of a tertiary care center. The study involved 73 participants and was completed over a duration of 18 months. **Results:** Majority of the subjects belonged to the age group of 18–25 years (54.79%), followed by 26–35 years (23.29%) and 36–45 years (10.96%). The mean age of the study subjects was 28.71 ± 10.72 years (median age –25 years). Most of the patients were male (82.19%). While majority of the subjects showed improvement with Non Steroidal Anti-inflammatory Drugs (NSAIDs) (80.82%), steroids were used among 12.33% subjects, sulfasalazine was used among 15.07%, and methotrexate among 1.37% of the study subjects. **Conclusion:** Statistically significant association was found between HLA B27 positivity and DAREA score, presence of sacroiliitis and extra-articular manifestation. NSAIDs remain the first line agents for patients with ReA. However, high baseline DAREA and ESR of more than 30 is associated with poor response to NSAIDs.

Key words: Sacroiliitis; Spondyloarthropathy; Synovitis

INTRODUCTION

Reactive arthritis (ReA) is a spondyloarthropathic disorder characterized by inflammation of the joints occurring either after a genitourinary or gastrointestinal infection. It is a sterile synovitis associated with infection at a distant site without evidence of sepsis at the affected joint and often associated with urethritis, conjunctivitis and occurrence of other extra-articular manifestations. Time interval between the onset of infection and joint symptoms should range from 1 week to a maximum of 4 weeks.¹⁻³ Clinical features are classically characterized by axial arthritis, oligoarthritis, and enthesitis accompanied by extra-articular manifestations. Musculoskeletal symptoms

are often acute and associated with systemic features such as fatigue, weight loss and fever. Extra-articular symptoms include mucocutaneous, ocular, and cardiac manifestations. Men and women are equally affected and the common age group is 20–40 years. Different bacterial species are associated with ReA. The most common enteric pathogens are Salmonella, Shigella, Campylobacter and Yersinia. Chlamydia trachomatis is the most common genitourinary pathogen.^{4,5} Factors contributing to etiopathogenesis include alternation in cytokine profile leading to impaired elimination of microbes, persistence of the microbe and trafficking of their antigenic peptides to the joint, leading to pathological immune response. Genetic factors are also known to play a role – 65–85% of ReA patients are positive

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for HLA-B27. The disease is more severe and chronic in these patients.^{6,7} Diagnosis of ReA is made on the basis of standard classification criteria and laboratory parameters. The treatment is in the form of rest, NSAIDs and intra-articular steroids. In chronic ReA, DMARD therapy is indicated. The role of antibiotic treatment is controversial. ReA is usually a self-limiting disorder; however, 15–30% may progress to chronic ReA (>6 months). Prognosis is less favorable in patients with HLA-B27 positivity.⁸⁻¹⁰

Aims and objectives

The study was conducted to assess the clinical, microbiological and laboratory profiles of patients with ReA in a tertiary healthcare centre and determine the outcomes (relapse/chronicity/symptom free) after a period of 3 months.

MATERIALS AND METHODS

A prospective analytical study was undertaken in the Rheumatology OPD of a tertiary care center. The study involved a sample size of 73 participants and was completed over a duration of 18 months. Patients over the age of 18 years and fulfilling the following criteria for diagnosis of ReA were incorporated in the study. Other causes of acute arthritis such as viral and septic arthritis, along with pregnant and lactating females were excluded from the study.

Diagnostic criteria (any two out of three including arthritis)

1. Patients presenting with asymmetric monoarthritis or oligoarthritis affecting predominantly the lower limbs.
2. Patients giving history of preceding symptomatic infection.
 - Enteritis (diarrhea for at least 1 day, 3 days to 6 weeks before the onset of arthritis).
 - Urethritis (dysuria or discharge for at least 1 day, 3 days to 6 weeks before the onset of arthritis).
3. Positive stool culture for enteric pathogens associated with ReA.

Permission from the Institutional Ethics Committee was taken and the study participants were incorporated only after obtaining a written informed consent. The patients' history and examination findings were noted with the help of a standard, semi-structured, and pre-validated case record proforma. Investigations as done by the treating physician and the treatment prescribed were noted down. However, no additional investigations were done solely for the purpose of study. Patients were followed up at the end of 3 months. The collected data was entered with the help of Microsoft Excel sheets. Statistical analysis was performed using the Chi-square test (for qualitative data)

and paired t-test (for quantitative data) with the help of SPSS version 21 software.

RESULTS

Majority of the subjects belonged to the age group of 18–25 years (54.79%), followed by 26–35 years (23.29%) and 36–45 years (10.96%). The mean age of the study subjects was 28.71 ± 10.72 years (median age of 25 years). Most of the patients were male (82.19%). The male: female ratio in the present study was 4.61:1. Joint pain was the most common complaint among all subjects (100% on admission and 82.19% on the 3 months follow-up), followed by joint swelling (100% and 68.49%), GI symptoms (61.64% and 0%), and fever (32.88% and 0%), as mentioned in Table 1.

The pain levels were recorded using the VAS scale. On admission, majority of the subjects had VAS score between 7 and 10 (50.68%) and 4 to 6 (49.31%). On follow-up examination after 3 months, 64.38% had a pain score in the range 0–3 and 32.88% had pain levels in the range 4–6. On admission, majority had tenderness of grade 1 (50.68%) followed by those with grade 2 (16.44%) and grade 3 (5.68%), which on follow-up was relieved in most patients (72.60%), while 27.40% of them still reported grade 1 tenderness. Joint swelling was observed among all subjects on admission, which was reduced to 30.14% on follow-up examination. Redness was noted among 1.37% subjects on admission, which was not noted in any patient on follow-up examination. It was observed that the range of motion was found to be decreased among 24.66% (on follow-up among 1.37%), urogenital involvement was seen among 2.74%, and mucocutaneous involvement was seen among 10.96% subjects, while ocular symptoms were noted among 6.85% subjects. Among the laboratory parameters, mean hemoglobin level was 12.33 mg/dl, mean WBC levels were 7449.17 per cu.mm, mean platelet level was 2.97 lakhs/ μ L, mean ESR level was 32.27 mm (12mm on follow-up), mean CRP level was 25.60 mg/L (9.26 mg/L on follow-up) and mean serum creatinine level was found to be 0.99 mg/dl (1.09 mg/dl on follow-up). We assessed the HLA B27 status among the study subjects. About 68.18% subjects tested positive, while 31.82% subjects tested negative for the same. The study subjects' mean DAREA score on admission was 31.95, while the same after follow-up examination after 3 months was 11.63. We compared and analyzed the scores using student t-test and observed the difference to be statistically significant (Table 2).

We observed that the mean DAREA score was 41.68 among HLA B27 positive subjects, and 29.43 among negative subjects. The association was found to be statistically significant (Table 3).

Table 1: Clinical presentation of the study participants on admission and at the time of 3 months follow-up

Clinical presentation	On admission		After 3 months	
	Number of subjects	Percentage	Number of subjects	Percentage
Joint pain	73	100.00	60	82.19
Joint swelling	73	100.00	50	68.49
Low backache	3	4.11	8	10.96
Enthesitis	9	12.33	0	0.00
Burning micturition	14	19.18	1	1.37
Urethral discharge	1	1.37	1	1.37
Skin lesions	4	5.48	1	1.37
Oral ulcers	4	5.48	2	2.74
Ocular symptoms	4	5.48	2	2.74
GI symptoms (AGE)	45	61.64	0	0.00
Fever	24	32.88	0	0.00
Other constitutional symptoms	2	2.74	1	1.37
Cardiopulmonary symptoms	0	0.00	0	0.00

Table 2: DAREA score of the study participants on admission and at the time of 3 months follow-up

Parameters	On admission	After 3 months
Joint swelling	1.74	1.13
Joint tenderness	1.589	0.411
Pain assessment	1.5	0.41
Global pain score	1.5	0.4
CRP	25.6	9.26
Mean DAREA score	31.95	11.63
Significance	t-value: -7.884367. The result is significant at P<0.05	

Among the subjects with ESR less than 30, mean DAREA score was 20.87, while among subjects with ESR more than 30, the mean DAREA score was 49.75. The difference was found to be statistically significant (Table 4).

Sacroiliitis was observed only among 9.58% study subjects. Almost all subjects having sacroiliitis had HLA B27 positive status. This association was found to be statistically significant (Table 5).

Ankle and knee were the most common joints to be involved (43.84% and 35.21% subjects). Digits were involved in 4.11% and wrist in 2.74% subjects. While the lower limb was commonly involved (89.04%), the upper limb was seen to be involved only in 10.96% subjects. Majority of the subjects with extra-articular involvement had HLA B27 positive status, but this association was not found to be statistically significant. In the present study, we also assessed the management among the study subjects. NSAIDs were used among all subjects. While majority of the subjects showed improvement with NSAIDs (80.82%), steroids were used among 12.33% subjects, sulfasalazine was used among 15.07%, and methotrexate among 1.37% of the study subjects.

DISCUSSION

Reiter¹ reported an early case of urethritis, conjunctivitis, and arthritis associated with spirochete infection. However, he was responsible for involuntary sterilizations, coerced euthanasia and medical experiments that outraged many in the scientific community. Thus, researchers have strongly recommended the name “Reactive arthritis” instead of “Reiter’s syndrome” due to Reiter’s unethical background. ReA is a sterile synovitis triggered by a distant infection of the genitourinary or gastrointestinal tract. Researchers have proposed its classification into HLA-B27-associated and non-associated forms and have observed a number of other clinical features in association with ReA. According to the criteria laid down by American Rheumatism Association, patients with ReA generally have asymmetric polyarthritis that lasts at least one month along with one or more of the following features: Urethritis, inflammatory eye disease, mouth ulcers, balanitis, or radiographic evidence of sacroiliitis, periostitis or heel spurs.

Lahu et al.,¹¹ in their study, discussed that ReA is illness that mostly affects male gender in ratio 2:1 in the cases of ReA of urogenital etiology, whereas situation with ReA of enteral etiology is different (frequency among genders is usually equal, with a slight domination of female gender). As for the age, our study indicates that most attacked group age is 20–40 years old, whereas under the age of 20 and over the age of 50 the illness is rarely seen. In a study by authors Villa et al.,¹² the youngest patient was a 13 years old; the literature indicates that ReA is rarely seen under the age of 9. Based on the epidemiological studies, association of ReA with acute gastrointestinal diseases (Salmonella, Campylobacter and Chlamydia) is 50%. In Shigella-induced ReA, association was seen in upto 80% cases. In 1998, Mattila et al.,¹³ revealed that the association of HLA-B27 with Salmonella Bovismorbificans was around 45%. Studies from England and Scandinavian

Table 3: Analysis of the DAREA score among HLA B27 positive and negative patients

HLA B27	Mean DAREA score	
	On admission	After 3 months
Positive	41.68	15.83
Negative	29.43	10.55
Significance*	t-value: 1.68808. The result is significant at P<0.05.	

Table 4: Correlation between DAREA score and ESR levels of the study participants

ESR	DAREA score	
	On admission	After 3 months
Less than 30	20.87	8.063
More than 30	49.75	17.37

Table 5: Presence of Sacroiliitis among HLA B27 positive and negative patients

HLA status	Sacroiliitis		Total
	Present	Absent	
Positive	6	9	15
Negative	1	57	58
Total	7	66	73
Significance	Chi-square value: 20.1396. The result is significant at P<0.05.		

countries showed 97% prevalence of HLAB27 in patients with ReA after Salmonella infections. Leirisalo-Repo et al.,¹⁴ showed in his study that 2 out of 9 patients developed spondyloarthropathy and they were associated HLA B27. In a study by Seiper et al., in 2002, the association of HLA B27 with enteric pathogens was about 50%. Ferrer et al., in their study, observed that, there was a higher than expected prevalence of sacroiliac (SI) joint tenderness (82% and 76% of patients reported tenderness in the right and left SI joints respectively), although low back pain has previously been reported as a common accompanying symptom in ReA. Uveitis was also highly prevalent in this population and resolved in most patients. An interesting finding was that nearly half of patients had persistent symptoms at 2 years. The present study did not find organisms in blood or urine culture reports. However, many outbreak studies have been published since 2000 on the outbreak of salmonella species and the ReA associated with it. In a study from USA by Dworkin et al., in 2001 on 217 patients with salmonella enteritidis, 29% patients developed ReA. However, none of the patients were associated with HLA-B27. In a study from Germany on 286 children with salmonella enteritidis by Rudwaleit et al.,¹⁵ in 2001, none of the patients developed ReA. In a study from Denmark in 2002 by Loch et al.,¹⁶ on 94 patients with Salmonella enteritidis, 19% of patients developed ReA. In a study by Hannu et al., from Finland in 2002 on 78 patients with

Salmonella typhimurium, 8% of patients had ReA. Two patients had association with HLA B27. He also concluded that the frequency of ReA after various enteric infections was around 10%. A Canadian-based study in 2005 by Lee et al., on 261 patients with Salmonella typhimurium showed that, 14.6% of patients developed ReA. HLA B27 was associated with 5/30 patients. An Australian study in 2008 by Rohekar et al., on 592 patients with Salmonella enteritidis revealed that, 19.2% patients developed ReA. 5/37 patients had association with HLA B27.¹⁷ General treatment of ReA still most commonly employs NSAIDs and sulfasalazine. Steroids are administered when the patient's inflammatory symptoms are resistant to the NSAIDs. Experience with other disease-modifying antirheumatic drugs, such as azathioprine, methotrexate, and cyclosporin, can be useful in treating patients who are unresponsive to the more usual medications. In more aggressive cases, TNF-alpha blockers could be an effective choice. The course of ReA probably varies considerably, depending on the triggering pathogen, the patient's genetic background and gender, and the presence of recurrent arthritis. Most patients remit completely or have little active disease 6 months after presentation. A European League Against Rheumatism study of 152 patients with ReA, who were enrolled within 2 months of the onset of arthritis, illustrated this well. By the end of an additional 24 weeks of observation, almost all patients had very low disease activity, as determined by physician and patient global assessments. After entering peripheral joint arthritis remission, patients occasionally note pain in the joints, at entheses, or in the spine. Chronic persistent arthritis, lasting more than 6 months, occurs in only a small proportion of patients. Children with ReA, who are positive for HLA-B27, have more severe involvement than children who are negative for HLA-B27.

CONCLUSION

Statistically significant association was found between HLA B27 positivity and DAREA score, presence of sacroiliitis and extra-articular manifestation. NSAIDs remain the first line agents for patients with Reactive Arthritis. However, high baseline DAREA and ESR more than 30 are associated with poor response to NSAIDs.

Limitations of the study

All causes of ReA were not included in the study (patients suffering from acute arthritis such as viral and septic arthritis were not a part of the study). This study involved the patients of a single tertiary care hospital.

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HJ- Review of literature and manuscript preparation, coordination, statistical analysis and interpretation; **SM, MN**- Concept and design of the study, Interpretation of results; **AM, HH, AG**- Statistical analysis and interpretation, preparation of manuscript and revision of the manuscript.

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