Immunogenetics of Inflammatory Arthritis in a Rural Population: COPCord Bhigwan (India)

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Introduction

Although the pathogenesis of this inflammatory autoimmune disorder has not been fully elucidated, rheumatoid arthritis (RA) is now understood as an entity with a strong genetic component, especially in the group of patients with erosions and seropositivity for rheumatoid factor (RF). Numerous contrary reports have emerged in this aspect.

The role of RF in the aetiopathogenesis of RA remains unclear. Although RF may be present before the onset of clinical disease, more usually RF is not detectable in serum until several months after onset and some patients with clinical RA remain persistently seronegative by conventional RF tests. The proportion of RA patients positive for RF has ranged from 30% to more than 90% in various studies\(^1\) and depends to a major extent on the definition of RA used in the clinic. Several population studies have derived varied conclusions concerning specificity / predictive value of RF testing. Prevalence of RF in a rheumatology clinic may be higher than in the community.

Associations between HLA-DRB1*04 and RF, a younger age of onset, increased disease severity and more erosive radiographic changes have been reported. The high occurrence of HLA DRB1*01 in RA patients of Indian origin residing in the UK has been reported\(^2\). However, Taneja et al\(^3\) have shown a higher association of HLA DRB1*04 with RA in their study on Indian patients. Absence of association of the seropositivity for RF and/or severity of RA with HLA DRB1*04 in the northern and southern Indian patients has been reported by Porkodi et al\(^4\). Detailed studies of HLA association with susceptibility to RA, seropositivity for RF or with severity of the disease have not proved to be sufficiently discriminatory to accurately define various subgroups in different ethnic population. Cross-sectional, unbiased prospective population studies are essential in order to define such associations at the molecular basis. Although many such population based studies have been reported, including some among the Asian Indians, the association of the HLA DR alleles with RA have shown to vary, leading to the Shared Epitope (SE) hypothesis. Also, one needs to explore the fact that, whether there is a difference in the HLA associations between community and clinical based RA.

Under the aegis of APLAR, the first Indian COPCord survey was conducted in village Bhigwan (Dist Pune) in 1996 followed by a well-planned ongoing community driven COPCord program till 2004\(^5\).

Methods

After interviewing 6034 villagers in the initial 1996 census survey 774 cases (Phase 1) reporting RMS (Rheumatic musculoskeletal pains) were identified\(^6\). Routine laboratory investigations for rheumatology work-up included complete blood count, Erythrocyte Sedimentation Rate (Westergren method), platelet count, Rheumatoid Factor by latex agglutination and Serum uric acid level. Kidney functions tests, liver function tests and antinuclear antibody testing was done as and when requested by the rheumatologist (AC). Laboratory investigations were done on 392 cases during the survey. 231 patients were investigated during the resurvey. More than 200 individuals from the village have been evaluated for various laboratory investigations since then till date as part of diagnostic work-up. Serum samples from all cases are being preserved at -70°C in the serum bank for any further analysis at. A positive test at a dilution of 1:40 and above was taken as positive for RF. 103 healthy individuals (HC) who were not suspected to be suffering from any rheumatic complaints were also tested for RF in order to determine the sensitivity and specificity of the test for RA.

Besides routine investigations for diagnosis of RA, we studied the HLA DRB1 profile of 156 individuals including 57 cases with inflammatory arthritis (IA), of whom 30 were unrelated RA cases, and 99 unaffected individuals from the same village who served as healthy controls.

10 ml blood was collected in sterile containers containing appropriate quantity of EDTA, and
stored at 4-8°C until they were processed. All whole-blood samples were air-transported to the ARC Epidemiology Unit, Manchester, where the HLA typing was done. HLA DRB1 alleles were determined using commercially available semi-automated PCS-SSOP typing systems (Inno-LiPA, Abbots UK and DynaRELI SSO, Dynal, UK).

Phenotype frequencies were calculated for the controls and compared with all IA patients using Odds Ratios with 95% confidence intervals.

**Observations**

1. **Rheumatoid factor**: 41% seropositivity was observed in the RA patients (N=27) with a mean value of 247 IU/ML (range 160-640 IU/ML). 31% of patients with erosive arthritis as evident in skiagrams (handsand/or feet) tested positive for RF. Among the non-inflammatory arthritis (NIA) group, 1.2% seropositivity was recorded (range: 80-160 IU/ML). The specificity of RF for RA by latex agglutination technique in our study was found to be 100% (versus IA-U); 98% (versus NIA) and 96% (versus HC).

The low sensitivity of RF (41%) in RA in this rural COPCORD is consistent with many other population surveys reported from different parts of the world. The high specificity of RF in the current study is rather reassuring.

2. **Antinuclear antibodies**: Positive ANA test was recorded in 1 patient of inflammatory arthritis who was clinically diagnosed as SLE during the follow-up. The prevalence of antinuclear antibodies in the current study was very low and is concordant with reports from other population study reports.

3. **HLA DRB1**: None of the DRB1 types were significantly associated with RF and erosions. No association of RA (p>0.05) with the shared epitope (SE) bearing alleles (HLA DR 1/4/10) alleles was observed(7). Although, the frequency of DRB1 10 was found to be higher (30%) in the inflammatory group as compared to the control group (20%). By contrast, in one hospital based study (unpublished)(8) conducted by us, 52 patients, (ARA Class II/III, RF + 83%, erosions 71%) of RA (classified as per ACR 1987 criteria) from our referral OPD were typed for HLA DRB1 alleles and compared with 77 healthy controls. The results of the latter showed an increase in the SE bearing alleles (56%; OR: 2.44; CI: 1.19-4.99) with a fairly good increase in DRB1 *10 (2.16%; OR: 2.16 CI; 0.96 – 4.84). These results suggest an increase in shared epitope bearing alleles in hospital based RA cases as compared with community based RA. The hypothesis that HLA-DR is associated with severity and not susceptibility in RA is evident from these data. However, the community data probably best reflects the ground reality.

**References**

3. Taneja V et al. HLA DR4- DQw8, but not DR5- DQw7 haplotypes occur in Indian patients with rheumatoid arthritis. Rheum Int 1992;11:251-5.
7. Chopra A et al. HLA DRB1 Association in a community based study of inflammatory arthritis in India. Arth Rheum 7 (Suppl) S71, 200.