Familial osteorarthritis : risk factors and determinants of outcome

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HLA-CLASS II IS ASSOCIATED WITH DISTAL INTERPHALANGEAL OSTEOARTHRITIS (DIPOA)

(Extended report)

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Abstract

Objective

To investigate whether there is an association between HLA-class II and distal interphalangeal osteoarthritis (DIP OA).

Methods

The study population consisted of consecutive patients with and without DIP OA between 40-70 years. DIP OA was diagnosed by radiology. These patients were referred to an "Early Arthritis Clinic" (EAC) with different types of arthritis in an early stage. Patients with RA, SLE, spondylarthropathies and psoriatic arthritis were excluded for the purpose of this study. DNA-typing for HLA-DR as well as X-rays of the hands were performed at enrolment in the EAC. In order to establish whether the study population was representative of the Dutch population we used as references, a population-based study in Zoetermeer (n=3243) for the prevalence of DIP OA and blood donors in the Leiden area (n=2400) for the HLA-DR antigen frequencies.

Results

Fifty-five patients (33.1%) of the total study population (n=166) had DIP OA. The frequencies of DIP OA and HLA-DR alleles were similar to the two reference populations. Within the study population, we found an association between DIP OA and HLA-DR2 and DR4 with respectively odds ratios of 2.4 (95%CI 1.1-5.0) and 0.3 (95%CI 0.1-0.7). No association was found between other HLA-DR alleles and DIP OA.

Conclusion

The study population is a representative sample of the Dutch population. The HLA-DR2 allele was more frequent in patients with DIP OA. Furthermore an inverse relationship was observed between DIP OA and HLA-DR4. Our results confirm findings from other investigations implicating HLA-DR2 as a risk factor in the development of DIP OA.

Key words

Hand Osteoarthritis, HLA-class II, genetics

Distal interphalangeal osteoarthritis (DIP OA), a subtype of OA, is a disease with a marked familial disposition. The role of genetics in hand OA was first noted by Stecher who found a clear hereditary basis for OA of the distal interphalangeal joints (DIP) of the fingers, based on the presence of Heberdens nodes, with sex and sib ship being important determinants.[1] Kellgren et al and Lawrence found a strong genetic component in the subset of patients with affected interphalangeal joints as assessed by radiology.[2] Furthermore, the notion of a genetic influence in nodal OA was confirmed by a subsequent twin study where heretability was estimated at 39-65%.[3]

Although genetics in hand OA have been the focus of many recent studies, up to this date, the genetic markers involved have not yet been identified. Among genetic markers examined in hand OA are markers on chromosome 6, the HLA-class I and HLA class II alleles. An increased frequency of the haplotype HLA-A1B8 has been suggested by several studies.[4][5] HLA-class II antigens have a highly polymorphic character and are associated with various diseases where inflammation of the joints plays a key role in the pathogenesis. Studies addressing the distribution of HLA-class II antigens render conflicting results. One study found a positive association between HLA-DR2 and DIP OA [6] and the other study found no association between HLA-class II and DIP OA.[7]

The diagnosis of hand OA in the past has been based on the presence of Heberden's nodes. However, more recent data indicate that radiological changes are more accurate to diagnose and grade the disease.[8] The prevalence of radiological hand OA in middle aged females in the age category of 50 to 54 years has been reported to be 42% in the DIP joints followed by 16% in the first carpometacarpal (CMC-1) joints and 10% in the proximal interphalangeal (PIP) joints.[9] The frequency of DIP OA increases with age peaking to a frequency of approximately 75% in 70 years olds.

The aim of the present study was to investigate the association of DIP OA with HLA-class II in patients aged between 40 to 70 years. We chose to limit ourselves to this age group for the following two reasons. The presence of OA before forty years of age is rare and is often exhibited in syndromes with a Mendelian segregation. In individuals older than seventy years old hand OA is mainly due to environmental factors.

Our study population is a series of consecutive hospital patients collected in a prospective manner. This population is representative of the general Dutch population since the frequency of DIP OA as well as the frequency of HLA-DR alleles is comparable to the two reference populations thus making it possible to investigate the relationship between HLA-DR and DIP OA within this population.

Materials and methods

Reference Populations

The prevalence of DIP OA and the distribution HLA-DR alleles in the study population were compared to two reference populations representative of the general Dutch population. As a reference for DIP OA data were used from the Zoetermeer population [9], a population survey consisting of 3109 men and 3476 women conducted between 1975 and 1978 in two districts of Zoetermeer,

a suburban metropolitan area near Leiden in the Netherlands. Persons in this study were documented for the presence of OA by radiographs of the hands, forefeet and lateral cervical spine. As a reference population for the distribution of the HLA-DR antigens, data were used from blood donors in the Leiden area who have been typed for HLA by serological methods. This is a population of circa 2400 persons.

Patients

The study population consists of subjects from the outpatient clinic of the Department of Rheumatology between the ages of 40 to 70 years old with and without radiological DIP OA. This population obtained between 1993 and 2000 is part of an ongoing project, the Early Arthritis Clinic (EAC). Consecutive patients with arthritis in at least one joint with a short history of complaints are admitted to this clinic by general practioners. Each patient subsequently undergoes full clinical, biochemical and radiographic assessment. Diagnoses in the EAC are made according to international classification and if necessary revised up to 1 year of follow-up.[10] For the purpose of this study, patients with a definitive EAC diagnosis after one year of follow-up are included. Patients with rheumatoid arthritis, systemic lupus erythematosus and spondylarthropathies were excluded because of known associations of these diseases with certain HLA-DR alleles. Patients with psoriatic arthritis were also excluded since DIP involvement is common in psoriatic arthritis and could thus interfere with our readings.

Radiographs and radiographic scoring

Plain dorsovolar hand radiographs were taken during the period of the first visit to the EAC. Only radiographs obtained at a maximum of 3 months before till 3 months after the first visit were included.
For the purpose of this study each of the radiographs was independently graded for DIP OA by two out of three observers (NR, JS, MK) using the Kellgren/Lawrence scale. Furthermore the radiographs are scored for the presence of DIP OA blinded for the underlying EAC diagnosis. This overall score distinguishes five degrees of severity of OA according to the presence of the radiological features: osteophytes, joint space narrowing (JSN), subchondral sclerosis, cysts and deformity. A patient was diagnosed with DIP OA if a Kellgren score of two or more was observed in at least one DIP joint. The inter-rater agreement for the presence or absence of DIP OA was 0.7; Cohen's kappa. In case of disagreement radiographs were re-evaluated until consensus was reached.

HLA-TYPING

DNA was isolated from blood lymphocytes. Generic DRB typing was performed with a polymerase chain reaction and biotin labelled sequence specific oligonucleotide (PCR-SSO) method as described previously.[11]

Statistics

The means were compared using an independent sample student-t-test. The observed (O) DIP OA frequencies in the study population, depicted for gender and age were related to the expected

number (E) in the reference population by calculating the O/E (a relative risk). Odds ratios (OR) with 95% confidence intervals (95%CI) were calculated to determine the comparability of the distribution of HLA alleles in the study population to the reference population and furthermore to assess the association between DIP OA and HLA-DR alleles.

Results

Six hundred and one consecutive patients between the ages of forty and seventy years visited the EAC. Of these patients 166 met the study criteria and were included in this study. The following patients were excluded: 64 patients were excluded because typing of HLA-DR had not been performed and 21 patients were excluded because no appropriate hand radiographs were taken. Furthermore, 240 patients were excluded with RA, 32 patients with psoriatic arthritis, 9 patients had a variety of systemic diseases and 69 patients were excluded because there was no definitive diagnosis made within one year.

The clinical characteristics of these patients are summarized in table 1. The patients in this study were included in the EAC with a broad variety of diagnoses. Fifty-five patients, 33% of our study population had DIP OA. 53% of the patients with DIP OA were females. The average age of patients with DIP OA was significantly higher than patients with no DIP OA respectively 57.7(SD$\pm$6.3) years compared to 49.2(SD$\pm$6.9) years ($p<0.001$). In table 2, the study population is compared to the Zoetermeer population depicted for age and gender. The prevalence of DIP OA is comparable to the reference population O/E 1.0 (95% CI 0.7-1.3).

Table 1. Clinical characteristics of the study population: patients with and patients without distal interphalangeal osteoarthritis (DIP OA)

	DIP OA (n=55)		**No DIP OA (n=134)**	
Average age (± SD)	57.7 (±6.3)		49.2 (±6.9)	
Gender (females)	53%		51%	
EAC diagnoses	septic arthritis	n=1	septic arthritis	n=1
	viral reactive arthritis	n=2	viral reactive arthritis	n=7
	crystal arthropathy	n=6	crystal arthropathy	n=7
	post-traumatic	n=0	post-traumatic	n=1
	osteoarthritis	n=14	osteoarthritis	n=6
	arthritis eci	n=24	arthritis eci	n=64
	para maligne	n=1	para maligne	n=3
	sarcoidosis	n=1	sarcoidosis	n=9
	other	n=6	other	n=11
	unknown	n=0	unknown	n=2

Table 2. Prevalence (%) of distal interphalangeal osteoarthritis (DIP OA) in females and males in the study population (n=166) in comparison to the Zoetermeer population (n=3243) depicted for gender and age categories

Age group (years)	DIP OA + (Study population)		DIP OA + (Zoetermeer population)	
	females	**males**	**females**	**males**
40-44	6.6(n=15)	0(n=15)	8.9(n=428)	8.6(n=395)
45-49	6.3(n=16)	6.7(n=15)	22(n=375)	14.1(n=353)
50-54	42.1(n=19)	34.8(n=23)	41.6(n=290)	24.0(n=309)
55-59	47.6(n=21)	50.0(n=10)	55.5(n=226)	40.5(n=216)
60-64	55.5(n=9)	66.7(n=9)	68.9(n=182)	48.9(n=174)
65-69	80.0(n=5)	66.7(n=9)	76.0(n=180)	51.7(n=115)

Table 3. The distribution of HLA-DR in the study population (n=166) in comparison to the blood donors (n=2400). This comparison is expressed in odds ratios and 95% confidence intervals (OR 95%CI)

HLA-DR alleles	Study population	Blood donors	OR(95% CI)
	Positive	**Positive**	
DR1	37	472	1.2 (0.8-1.7)
DR2	37	688	0.7 (0.5-1.1)
DR3	41	598	1.0 (0.1-1.4)
DR4	51	679	1.1 (0.8-1.6)
DR5	35	453	1.1 (0.8-1.7)
DR6	59	806	1.1 (0.8-1.5)
DR7	31	460	1.0 (0.6-1.5)
DR8	7	128	0.8 (0.3-1.8)
DR9	4	57	1.0 (0.3-2.9)
DR10	6	101	0.9 (0.3-2.0)

The distribution of HLA-DR in the study population in comparison to the Leiden blood donors is summarized in table 3. No significant difference was found in the distribution of the HLA- DR between the two groups as is demonstrated by the odds ratio's of around one for each separate DR antigen.

The association between DIP OA and HLA-DR in the study population is shown in table 4. An association is found between DIP OA and HLA-DR 2 and HLA-DR 4 with odds ratios of respectively 2.4 (95% CI 1.1-5.0) and 0.3 (95% CI 0.1-0.7). No association with the other HLA-DR antigens and DIP OA was observed.

Table 4. Association of HLA- DR with distal interphalangeal osteoarthritis (DIP OA) within the study population (n=166) in patients with and patients without distal interphalangeal osteoarthritis (DIP OA)expressed as odds ratios with 95% confidence intervals (OR 95% CI)

HLA- DR alleles	DIP OA + (n=55)		DIP OA – (n=111)		OR (95% CI)
	present	absent	present	absent	
DR1	14	41	23	88	1.3(0.6-2.8)
DR2	18	37	19	92	2.4(1.1-5.0)
DR3	13	42	28	83	0.9(0.4-2.0)
DR4	9	46	42	69	0.3(0.1-0.7)
DR5	12	43	23	88	1.1(0.5-2.3)
DR6	19	36	40	71	0.9(0.5-1.8)
DR7	10	45	21	90	1.0(0.4-2.2)
DR8	2	53	5	106	0.8(0.2-4.3)
DR9	2	53	2	109	2.1(0.3-15.0)
DR10	2	53	4	107	1.0(0.2-5.7)

Discussion

The aim of the present study was to investigate the association of HLA-DR with DIP OA. We found that HLA-DR2 was more frequent in patients with DIP OA than in patients with no radiological evidence of DIP OA with an OR of 2.4 (95% CI 1.1-5.0). We also found a lower prevalence of DIP OA in HLA-DR4 positive patients with an OR of 0.3 (95% CI 0.1-0.7). This is to our knowledge the first time that an association with HLA-DR4 has been established. Other investigators have suggested the positive association with HLA-DR2.

We had the unique opportunity to study the relationship of these two variables in a relatively large group of well-documented patients representative of the general population. This consecutive patient population was collected in a prospective manner and HLA- typing and radiological X-rays were performed irrespective of the EAC diagnosis. Because the study population consisted of patients included in an early arthritis clinic we took into consideration the existing correlation between certain rheumatic diseases and HLA alleles while selecting the patients for the present study. Patients with diagnoses with known HLA associations and diseases associated with radiological damage of the DIP joints, such as psoriatic arthritis were excluded from the study population. Although radiological damage would not have been very likely since patients are included in the EAC in a very early stage. Furthermore, it was demonstrated that the study population is a representative sample of the general population by finding in this population similar frequencies of DIP OA and HLA antigens.

Only two studies, up till now, have investigated the correlation between HLA class II antigens and hand OA with conflicting results.[6][7] These studies were performed in ethnically separate groups, a group of Ashkenazi Jews and a group of Mexican Mestizos. The Ashkenazi Jews study was performed with a small group of patients with clinical characteristics of hand OA and controls consisting of "healthy individuals". They found a positive association with HLA- DR2, although this association was not significant. It is possible that the limited sample size may have attributed to not finding significant results in this study. The second publication studied the relationship between Heberden's nodes and HLA in a group of Mexican Mestizos. The authors of this study found no association between these two variables. This may have been caused by using different diagnostic criteria of hand OA in patients versus controls. Patients were diagnosed with hand OA on the basis of the combination of clinical and radiographic characteristics while the controls were screened for the absence of Heberden's nodes without radiological assessment. Since there is a discrepancy between signs and symptoms versus radiological manifestations of OA, as is demonstrated in patients with radiological OA showing symptomatic disease in 20 to 40% of the cases, the absence of radiological assessment of the control population could have led to an under-diagnosis of OA in the reference population used in this study. Recently further evidence of the role of HLA-DR2 as a risk factor for DIP OA was observed in two European populations, one in Germany [12] and the other in Iceland [Jonsson H.H., personal communication].

No earlier study has found an association with HLA-DR4 and hand OA. Therefore, further studies in other populations are needed to confirm these results and to rule out the possibility of a false positive association (type 1 error) because of multiple testing.

One may hypothesize a direct role of HLA-DR antigens in OA. HLA-class II molecules are involved in the communication between T cells and antigen-presenting cells. Although OA is not generally considered to be an autoimmune disorder with an inflammatory nature, several studies suggest a role for T-cells and HLA class II molecules in OA. One study on the synovial membranes of patients with OA indicates T-cell mediated immune responses in this disorder.[13] Another recent study demonstrated higher levels of human cartilage glycoprotein 39 (HC gp-39) specific T cells, in patients with OA than in healthy controls.[14] Furthermore, activated T-cells have been suggested to play a role in bone metabolism and osteoclast regulation via the Rank-L molecule. This interaction may directly lead to bone formation.[15]

Another possibility is that the role of HLA- class II alleles implicated in this study is due to linkage disequilibrium with neighboring genes of HLA- DR class II alleles which may be involved in the pathogenesis of OA. Whether our findings are a matter of haplotype or whether they implicate a direct role for HLA-DR alleles needs to be further investigated.

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