Clinical and Genetic Study of Juvenile Rheumatoid Arthritis

Elham Ragab Abd El Samee[1] ,Farha El Chennawy[1], Ahmed Yehya Al Shambaky[2]

1. Clinical Pathology Department, Faculty of Medicine, Mansoura University
2. Rheumatology & Rehabilitation Department, Faculty of Medicine, Benha University
elhamelngar@yahoo.com

ABSTRACT: Juvenile rheumatoid arthritis consists of a group of childhood onset Rheumatic disease having in common chronic inflammation of one or more joints. The subtypes of juvenile rheumatoid arthritis differ in clinical manifestations, prognosis and specific immunological features. Genetic and environmentally associated determinants interact, contributing to the development and pathogenesis of juvenile rheumatoid arthritis. A characteristic feature of juvenile rheumatoid arthritis is the interaction of HLA genes within the same locus or between different loci that increases the risk of the disease. Some HLA associations are due to linkage disequilibrium between markers involved, but accumulating evidence indicates that several different genes in the HLA region are implicated in the pathogenesis of juvenile rheumatoid arthritis. To determine the association of human leukocytic antigen (HLA) class I and class II with juvenile rheumatoid arthritis in Egyptian children and its relation to clinical and laboratory findings. Fifty Egyptian children patients with JRA and 40 controls were included. They were subjected for complete clinical examination and Laboratory investigation. Rheumatoid factor (RF) was performed using latex test while antinuclear antibodies (ANA) were measured by ELISA. For HLA-class I typing, lympho-microcytoxicity technique was performed, while for HLA class II typing, PCR-SSOP using innolipa was used. There was significant positive association of JRA patients with HLA class I, HLA-A10, HLA-B (B13, B27, B35), and class II, HLA-DR B1 alleles (*0101, *0102, *0801 and *1104), HLA-DQA1 alleles (*0401), and HLADQB1 alleles (*0202, *0303, *0603-09). While HLA-B12 and HLADQB1 *0602 were significantly positive associated with healthy controls, also there was positive association between HLA-DQA1 *0501 and HLA-DQB1 *0603 and pauciarticular onset JRA while polyarticular type was positive associated HLADQA1 *0101. A significant positive association was found between ANA positive patients and HLA-DRB1 *1104 allele.
Conclusion: We conclude that there are some associations of HLA markers with JRA and its clinical manifestation.
[Abd El Samea ER, El Chennawy F, Al Shambaky AY: Clinical and Genetic Study of Juvenile Rheumatoid Arthritis. New York Science Journal 2011;4(4):8-15]. (ISSN: 1554-0200). http://www.sciencepub.net/newyork.

Key words: Rheumatoid arthritis, human leukocytic antigen (HLA), Rheumatoid factor

INTRODUCTION

Juvenile idiopathic arthritis is a heterogeneous condition classified into different subtypes according to the symptoms at onset. Oligoarticular juvenile idiopathic arthritis is the most frequent form (26% to 56% of all juvenile idiopathic arthritis) and is characterized by early disease onset, asymmetric arthritis, high prevalence of iridocyclitis, peculiar HLA association (HLA-DRB1*1101, DRB1*0801, DPB1*0201), and the presence of antinuclear antibodies. In the majority of these patients, the disease remains confined to a limited number of joints (persisted oligoarticular juvenile arthritis) and has a favorable outcome characterized by a high frequency of self-remission[(1)]. Approximately one third of patients with oligoarticular onset experience progression toward a more aggressive form, characterized by involvement of five or more joints after the first six months of disease (extended oligoraticular juvenile idiopathic arthritis) in 10% to 30% of juvenile idiopathic arthritis patients, the disease shows symmetric involvelment of more than four joints, with erosive course during the first 6 months of disease (polyarticular-onset juvenile idiopathic arthritis). A small proportion of these patients (3% to 5% of all juvenile idiopathic arthritis patients) display positivity for rheumatoid factor (RF). The systemic-onset juvenile idiopathic arthritis is observed in 4% to 17% of patients and is characterized by a severe systemic involvement (rash, fever, hepatosplenomegaly) associated with arthritis of variable severity that may evolve into an aggressive polyarticular course ***(Ravelli and Martini, 2007)***. A distinctive feature of chronic inflammatory arthritides is the presence of synovial lymphocytic infiltrates that play a role in disease pathogenesis through the release of pro-inflammatory cytokines and other soluble mediators ***(Muller-Ladner et al., 2005)***. Genes in the major histocomaptibility complex of humans, termed HLA, are known to influence susceptibility to over 300 diseases. These include: complex autoimmune and inflammatory disease such as type 1 diabetes, rheumatoid arthritis, ankylosing spondilitis, psoriasis, multiple sclerosis and narcolepsy; nasopharyngeal

cancer, Hodgkin disease and other cancers; infectious disease including malaria, tuberculosis, and AIDS, and disease of unknown etiology. HLA allele or haplotype and genotype associations with specific disease are well established; the most complex pattern is seen with type 1 diabetes and HLA DRB1-DQB1 haplotypes, with a hierarchy from very predisposing, through intermediate ("neutral"), to very protective effects, with consistent patterns in associations seen across ethnic groups ***(Thomson et al., 2007)***. The strong association of the HLA DRB1 "shared epitope" set of AAs 70-74 and rheumatoid arthritis is well established; recently autoimmunity to citrullinated protein antigens has been shown to define a clinically and genetically distinct subset of rheumatoid arthritis that is specifically associated with the "shared epitope" alleles ***(Imboden 2009)***. The recent development of a novel approach to genetic association analyses with genes/proteins sub-divided into biologically relevant smaller sequence features, and their variant types ***(Karp et al., 2009)***, allows a systematic search focusing on the most likely actual causative genetic variants in HLA associated disease. Juvenile rheumatoid arthritis is the most frequent major rheumatic disease of children ***(Cassidy and Petty, 2000))***. It is a complex polygenic disease and genetic determinant may also vary among the subtypes ***(Forre and Smerdel, 2002)***. It is one of the more common chronic illness of childhood and is the major cause of functional disability. Early diagnosis is facilitated by recognition of the three major types of presentation: Oligoarthritis (60% of the case), polyarthiritis (30%), systemic disease (10%), large joints, subcutaneous nodules and rheumatoid factor (RF) seropositivity are unusual, but antinuclear antibody (ANA) seropositivity is a hallmark of the disease ***(Ravelli and Martini,2007)***. There are two principal sets of criteria for children with chronic idiopathic arthritis of the peripheral joints: that for "juvenile rheumatoid arthritis" of the American College of Rheumatology ***(Cassidy et al., 1986)*** and that for "juvenile chronic arthritis" of the European league against rheumatism. JRA begins at or before the age of 16 years, the onset before 6 month of age is unusual, the age at onset is characteristically young but substantial number cases begin throughout childhood. Although JRA seldom occurs in siblings, data on human leukocyte antigen (HLA) segregation underscore a hereditary basis. There is a striking increase in the frequency of HLA-A2 and specific HLA-DR, DQ and DP genotype associated eith the type of onset and course subtype. The HLA antigens DR5 (DRB1 1104), DRw6, DRw8, DQw1 (DGAi 0501), and DGw2 (DpB 0201) are associated with the development of persistent oligoarthritis at an early age in young girls with ANA seropositivity ***(Hass et al., 1994)***. The aim of this work is to determine the association of HLA with JRA and its clinical manifestation.

PATIENTS and METHODS:

This study was carried on fifty children collected from Benha and Mansoura University hospitals, all patients are fulfilling the criteria of ACR for JRA ***(Cassidy et al., 1986)***. They were thirty four female and sixteen males. All patients were subjected for: Full history taking from the parents (stressing on: Number and sequence of joints affection at the onset, Duration of the disease, Morning stiffness, Associated systemic manifestation); Complete clinical examination (including articular index for tenderness ***(Ritchie et al., 1968)***; Slit Lamp examination; Laboratory investigation (including: Full blood picture measured by coulter, Erythrocyte sedimentation rate [ESR] was determined by westergreen method, C-Reactive Protein [CRP] by latex agglutination using SPINREACT, S.A. Espana; Rheumatoid Factor [RF] by latex agglutination using SPINREACT, S.A. Espana; Antinuclear antibodies (ANA) was measured by ELISA kit using commercial Kallestad microplate EIA); Plain x-ray on involved joint groups; HLA typing.

For antigens of class I performed by the lymphocyte microcytoxicity test ***(Terasakio et al., 1978)***. The figure of control samples were taken from HLA-class I antigens in the Egyptian population, 380 case for HLA class 1 ***(Hafez and El-Shennawy,1986)***. HLA typing for class II was performed by PCR-SSOP methods using Innolipa (Innogenetics-Belgium). This test is based on reverse hybridization principle ***(Buyse et el., 1993 and Thonnard et al., 1995)***. DNA is first extracted from the test sample, then amplified using the polymerase chain reaction. The amplified brotinylated DNA is chemically denatured and the single strands are hybridized with specific oligonucleotide probes immobilized as parallel lines on membrane-based strips.

After hybridization, alkaline phosphatase-labeled strepavidine is added incubation with chromogen results in a purple brown precipitate, indicating biotinylated DNA. The reaction is stopped by wash step and the reactivity pattern of probes is recorded. The site and molecular weight of the hybridized probe define a certain allele.

A control group- consisted of 40 healthy unrelated blood donors residing in the same geographical area and representing the same ethnic background as the patients- was included in HLA class II study.

The patients were clinically divided into subgroups according the type of JRA: Polyarticular onset group and consisted of 8 patients; Systemic onset group and consisted of 7 patients; Pauciarticular onset group and consisted of 35 patients.

Statistical analysis was done by using SPSS (statistical pelage for social science program version 10, 1999). The quantitative data were expressed as a number and percentage. Chi-square with Yates correction was used as a test of significance for qualitative data. Student t test was used to study significance of quantitative data. Odds ratio and confidence interval were calculated to study the risk of the development of the disease. Kolmogrove-Smirnov test was done to prove data were parametric. Significance was calculated according to P value. P value less than 0.05 is considered significant. P value more than 0.05 considered insignificant.

RESULTS;

The mean age of the patients was 7.34 ± 3.38 years while the duration of the disease was 2.46 years ± 1.09, Uveitis was positive in 4 patients (8%), ANA was positive in 16 (32%), RF was positive in 8 patients (16%) (table 1). A significant increase in the frequency of HLA-A10, HLA-B (B13, B27, B35) was detected in JRA patients than controls (HLA, A10=6%, B13=12%, B27=14% and B35=8%) while HLA-B12 was significantly more frequent in controls than patients (in control 20.5% while in patients=8%). (table 2) A statistically significant association of HLA-DRB1 alleles (*0101=16%, *0102=16%, *0801=18% and *1104=10%) with patients than controls was detected, while HLA-DRB1 *1501 was more frequent in control (10%) than patients (4%). A significant positive association of HLA-DQA1 *0401 with patients (14%) more than controls (0%) was detected, (table 3), while HLA-DQA1 *0201 and *0603 were more frequent in controls than patient without statistical significance. (HLA-DQA1 *0201 in controls=15% while in patients=6%, and *0603 in controls=7.5% while in patients=0%). Also the distribution of HLA-DQB1 alleles in patients (*0202=16%, *0303=14% and *0603-09=24% for each) was significantly more frequent than in controls (0% for each). While HLA-DQB1 *0602 was statistically more frequent in controls (25%) than patients (5%) (table 3). In polyarticular onset JRA, HLA-DQA1 *0101 was more frequent, while in pauciarticular onset group, HLA-DQB1 *0603, HLA-DRB1 *0801 and HLA-DQA1 0501 were more frequent but without statistical significance (table 4). Significant association between HLA-DRB1 *1104 allele and ANA positive patients were detected (80% in the ANA positive patients, 20% in negative patients) (table 5).

Table (1) Showing Clinical and Laboratory data of the patients

Types of JRA		
Polyarticular	n=8	16%
Systemic	n=7	14%
Oligoarticular (pauciarticular)	n=35	70%
Mean age ± SD (yr)	7.34 ± 3.38	
Mean duration of the disease ± SD (yr)	2.46 ± 1.09	
Gender		
Male	n=16	32%
Female	n=34	68%
Uveitis		
+ve	n=4	8%
-ve	n=46	92%
Mean of M.S ± SD (min)	25.62 ± 12.08	
Mean Hb ± SD (gm)	10.96 ± 1.47	
ANA		
+ve	n=16	32%
-ve	n=34	68%
RF		
+ve	n=8	16%
-ve	n=42	84%
Mean ESR ± SD	23.76 ± 8.37	
Mean AI ± SD	9.32 ± 4.24	
RF= Rheumatoid factor	M.S.= morning stiffness	
A.I= Articular index	JRA= juvenile rheumatoid arthritis	
N= number of patients		

Table (2) shows HLA class I (HLA-A, HLA-B) in patients and control

HLA Class I	Patients		Control		Test of Significance P
	n	%	n	%	
HLA-A					
A1	10	20	76	20	0.85
A2	11	22	112	29.5	0.27
A3	5	10	31	8.2	0.65
A9	1	2	34	8.9	0.065
A10	3	6	0	0	<0.001*
A11	4	8	49	12.9	0.55
A13	1	2	0	0	0.11
A21	1	2	0	0	0.11
A28	2	4	31	8.2	0.23
A41	1	2	0	0	0.11
HLA-B					
B5	13	26	67	17.6	0.15
B10	1	2	0	0	0.11
B12	4	8	78	20.5	0.034*
B13	6	12	12	3.2	0.011*
B21	3	6	21	5.5	0.54
B27	7	14	18	4.7	0.017*
B28	1	2	0	0	0.11
B35	4	8	0	0	<0.001*

*P<0.05: Statistically significant

Table (3) shows HLA Class II among patients and control

HLA Class II	Alleles	Patients=50		Controls=40		P	Odds' ratio confidence interval
		n	%	n	%		
HLA-DRB1	0101	8	16	0	0	0.008*	
	0102	8	16	0	0	0.008*	
	0201	0	0	1	2.5	0.26	
	0301	5	10	2	5	0.37	0.32 $\overset{2.11}{\_\_\_\_}$ 23.1
	0401	4	8	0	0	0.067	
	0404	1	2	0	0	0.36	
	0701	2	4	2	5	0.81	1 $\overset{8.56}{\_\_\_\_}$ 384.1
	0801	9	18	1	2.5	0.021*	
	0901	1	2	0	0	0.36	
	1001	1	2	0	0	0.36	
	1010	1	2	0	0	0.36	
	1104	5	10	0	0	0.039*	
	1301	6	12	4	10	0.47	
	1404	1	2	0	0	0.36	0.03 $\overset{0.38}{\_\_\_\_}$ 2.81
	1501	2	4	4	10	0.25	
	1601	3	6	0	0	0.115	
HLA-DQA1	0101	4	8	0	0	0.09	
	0201	3	6	6	15	0.29	0.07 $\overset{0.47}{\_\_\_\_}$ 2.37
	0301	7	14	8	20	0.55	0.18 $\overset{0.65}{\_\_\_\_}$ 2.31
	0302	2	4	3	7.5	0.47	0.04 $\overset{0.51}{\_\_\_\_}$ 4.76
	0303	0	0	3	7.5	0.08	
	0401	7	14	0	0	0.013*	
	0402	0	0	3	7.5	0.08	0.78 $\overset{4.17}{\_\_\_\_}$ 41.5
	0501	9	18	2	5	0.061	0.02 $\overset{0.24}{\_\_\_\_}$ 1.45
	0502	2	4	6	15	0.068	0.10 $\overset{0.79}{\_\_\_\_}$ 6.24
	0601	3	6	3	7.5	0.77	
	0602	0	0	3	7.5	0.08	
	0603	0	0	3	7.5	0.08	
	0606	1	5	0	0	0.36	

HLADQB1	0201	8	16	3	7.5	0.22	
	0202	8	16	0	0	0.009*	0.51 2.35 14.62
	0301	0	0	3	7.5	0.08	
	0302	0	0	3	7.5	0.08	
	0303	7	14	0	0	0.015*	
	0304	0	0	2	5	0.15	
	0401	7	14	3	7.5	0.32	0.42 2.01 12.7
	0402	7	14	2	5	0.15	0.54 3.09 31.92
	0501	4	8	3	7.5	0.92	0.17 1.07 7.78
	0502	2	2	2	5	0.81	0.06 0.79 11.42
	0601	3	15	0	0	0.115	
	0602	1	5	10	25	0.001*	0 0.04 0.93
	0603	12	24	0	0	0.008*	
	0604	12	24	0	0	0.008*	
	0605	12	24	0	0	0.008*	
	0606	12	24	0	0	0.008*	
	0607	12	24	0	0	0.008*	
	0608	12	24	0	0	0.008*	
	0609	12	24	0	0	0.008*	

*P<0.05 is significant

Table (4) show HLA Class II alleles in different types of JRA

HLA Class II		Oligoarticular =35		Systemic=7		Polyarticular=8		p
		n	%	n	%	n	%	
HLA-DRB1	0101	5	14.3	1	14.3	2	25	0.76
	0102	5	14.3	1	14.3	2	25	0.76
	0301	3	8.6	1	14.3	1	12.5	0.81
	0401	3	8.6	1	14.3	0	0	0.25
	0404	1	2.9	0	0	0	0	0.81
	0701	2	5.7	0	0	0	0	0.41
	0801	7	20	1	14.3	1	12.5	0.35
	0901	1	2.9	0	0	0	0	0.81
	1001	1	2.9	0	0	0	0	0.81
	1010	0	0	0	0	1	12.5	0.76
	1104	5	14.3	0	0	0	0	0.32
	1301	4	11.4	0	0	2	25	0.35
	1404	1	2.9	0	0	0	0	0.81
	1501	1	2.9	1	14.3	0	0	0.23
	1601	1	2.9	1	14.3	1	12.5	0.30
HLA-DQA1	0101	1	2.9	0	0	3	37.5	0.051*
	0201	3	8.6	0	0	0	0	0.52
	0301	5	14.3	1	14.3	1	12.5	0.97
	0302	2	5.7	0	0	0	0	0.67
	0401	5	14.3	1	14.3	1	12.5	0.97
	0501	7	20	1	14.3	1	12.5	0.34
	0502	2	5.7	0	0	0	0	0.67
	0601	3	8.6	0	0	0	0	0.52
	0606	1	2.9	0	0	0	0	0.81
HLA-DQB1	0201	5	14.3	2	28.5	1	12.5	0.48
	0301	5	14.3	0	0	2	25	0.41
	0303	5	14.3	0	0	0	0	0.38
	0401	5	14.3	1	14.3	1	12.5	0.97
	0501	4	11.4	0	0	0	0	0.41
	0502	2	5.7		0	0	0	0.71
	0601	1	2.9		14.3	1	12.5	0.51
	0602	1	2.9	0	0	0	0	0.81
	0603	7	20	2	28.5	3	37.5	0.50

*P<0.05 is significant; n= number of patients

Table (5) shows correlation between HLA Class II significant alleles and some clinical and laboratory data

HLA Class II Alleles	Some clinical and laboratory data										
	Uveitis				ANA				Age of onset	M.S	A.I
	+ve		-ve		+ve		-ve				
	n	%	n	%	n	%	n	%			
HLA-DRB1											
0101	0	0%	8	100%	1	12.5%	7	87.5%	9.62 ± 3.24	15.62±12.08	9 ± 4.44
0102	0	0%	8	100%	1	12.5%	7	57.5%	9.62 ± 3.24	25.62±12.08	9 ± 4.44
0801	1	11.1%	8	88.9%	4	44.4%	5	55.6%	6.41 ± 2.61	19.44±11.30	8.22 ± 9.02
1104	1	20%	4	80%	4	80%	1	20%	6.24 ± 3.37	21 ± 13.87	7.2 ± 3.03
HLA-DQA1											
0401	2	28.5%	5	71.5%	1	28.5%	5	71.5%	6.25 ± 3.03	26.25 ± 9.46	9.5 ± 3
HLA-DQB1											
0201	2	25%	6	75%	2	25%	6	75%	7.12 ± 3.52	29.3 ± 9.03	10.25 ± 3.41
0303	0	0%	5	100%	1	20%	4	80%	8.84 ± 4.8	17 ± 7.58	7.6 ± 3.91
0603	2	16.7	10	83.3%	5	41.7%	7	58.3%	6.95 ± 3.10	27.5 ± 10.11	9.83 ± 3.38

*P<0.05 is significant

DISCUSSION

HLA molecules are cell-surface proteins that present peptide fragments to T-cell to activate the recognition, and response to, foreign antigens. The classical class I (HLA-A, -B and –C) and class II (HLA-DR, -DQ and –DP) genes encode structurally homologous heterodimers. The processed self and foreign peptide fragments presented by the classical HLA molecules usually consist of 8-10 AAs (class I) or 12-20 AAs (class II), and are of either intracellular or extracellular origin respectively. An HLA molecule binds only to peptides conforming to certain structural requirements. A particular HLA alleles is thus only able to present a subset of the available peptides to T-cells. The polymorphism of many of the HLA genes is extraordinary, with over 3,000 alleles at the class I and class II genes identified to date, with much of the variation present at the protein level and occurring at functionally important sites. The class II HLA DRB1 gene, has 623 alleles defined at the AA level; for any specific population or disease study only a fraction of these alleles will be observed. There are multiple lines of evidence for the role of balancing selection (at the allele and AA levels) in maintaining this most polymorphic set of genes in the human genome, including relatively even allele frequency distributions. The casual argument presented is that individuals heterozygous for HLA genes can more effectively defend themselves from infection by successfully responding to a broader range of pathogens ***(Solberg et al., 2008)***. Juvenile rheumatoid arthritis is a group of heterogeneous inflammatory arthritis of childhood in which several level of the disease phenotypes have well established HLA-associated risks described population-association studies ***(Fernando et al., 2008 and Smollen & Aletha 2009)***. This study was planned to determine the association of HLA antigens with JRA and clinical and laboratory findings in JRA patients. Our results revealed that frequencies of HLA class I antigen A10, B13, B27 and B35, are significantly increased in patients with JRA compared to the control group while HLA B12 is significantly higher in controls than patients, these results suggest that patients bearing these HLA molecules (HLA class I, A10, B13, B27, B35) have increased susceptibility to develop JRA while HLA-B12 appears to be a protective one. Our results agree with that reported by ***(Marta et al., 1998)*** who concluded that HLA-B27 and B35 are significantly associated to JRA. In our study we find also HLA A10, B13 increased in patients compared to control while *MARTA* found- in addition to HLA B27, B35- that HLA A2 is more frequently in his patients-while HLA-A2 was insignificant in our patients. In a similar study done by ***Abdul Al Rehiem et al., 2002***, they found that HLA-B12 was more frequently segregated in healthy controls than patient, this is approved also in our study, while HLA-A2 in their study was significantly increased in their patients in contrast to our findings. We also observed that HLA B27 is significantly increased in our patients which are also documented in several other studies ***(Pyruber et al., 1996 and Albert & Scholz, 1998)***. Also the frequency of HLA class II alleles DRB1 *0101, 0102, 0801 and 1104 were significantly increased in JRA patients than control while *1501 was increased in control than patients. Our results are similar to this study done by ***Abdul Al Rehiem et al., 2002*** as regard significant association between JRA and HLA-DRB1 *0801, 0101 which also approved by ***Albert & Scholz, 1998; Rundstaller et al., 2003; Glass 2010; and van der Helm-van et al., 2006***. High association of HLA DRB1*0101, *0404 in individuals of European ancestry or *0405 and *0901 in Asians ***(Rumba et al., 1997)***. In the present study, the alleles of HLA-DQA1

(*0401) and alleles of HLA-DQB1 (*0303, *0202, *0603/09) were significantly increased in JRA patients than controls while HLA-DQA1 *0201 and *0603 nonsignificantly increased in controls than patients. Also we found that HLA-DQB! Alleles (*0602) was significantly increased in controls than in patients, these results are comparable to the results obtained by ***Abdul Al Rehiem et al., 2002*** where the two studies showed significant increase of HLA-DQA1 0401 DQB1*06(03-09) alleles in the patients than in controls. Also these results go hand in hand with the study done by ***Gertsi et al., 1999 and Turesson & Matteson 2009***, further analysis of the results of this present study showed non significant association between HLA-DRB1 alleles and types of JRA, while HLA-DQA1 *0101 is highly associated with polyarticular type and DQA1 *0501 is highly associated with pauciarticular type but without statistical significance of both. Also there was increase association DQB! *0603 with pauciarticular type without reaching statistical significance. This results- to some extent- agree the results reported by ***Abdul Al Rehiem et al., 2002*** where we found significant association DQA1 *01 with polyarticular JCA and DQA1 *0501 was positively associated with seronegative subset while in our study DQA1 *0501 was positively associated with pauciarticular JRA, as well as DQB1 *06 was more frequent in apuciarticular type in the two studies. We found that HLA-DRB1 *1104 was significantly more frequent in ANA positive patients, these results are similar to that obtained in other groups studied by ***Gertsi et al., 1999***. Major organ manifestations have become less frequent in clinical practice ***(Turesson and Matteson, 2009)***. We concluded that there are some associations of HLA markers with JRA and its clinical manifestations.

Corresponder:
Elham Ragab Abdul Samea
Assistant professor in Clinical Pathology
Department of Clinical Pathology
Mansoura University, Egypt
Tel. 0114571726
Email: elhamelngar@yahoo.com

REFERENCE:

1. **Ravelli A, Martini A (2007):** Juvenile idiopathic arthritis. Lancet. 369: 767-778
2. **Muller-Ladner U, Pap T, Gay RE, Neidhart M, Gay S (2005):** Mechanisms of disease: the molecular and cellular basis of joint destruction in rheumatoid arthritis. Nat Clin Pract Rheumatol. 1: 102-110
3. **Thomson G, Valdes JA, Noble JA et al., (2007):** Tissue Antigens. 70: 110
4. **Imboden JB (2009):** Annu. Rev. Pathol. Mech. Dis. 4: 417
5. **Karp DR, Marthandan N, Marsh SGE et al., (2009):** Hum. Mol. Genet. Under revision
6. **Cassidy JT and Petty RE (2000):** Juvenile Rheumatoid Arthritis. Text book of pediatric Rheumatology, 4th Ed. Philadelphia, WB Saunders
7. **Forre O, Smerdel A (2002):** Genetic epidemiology of juvenile idiopathic arthritis. Scand J Rheumatol. 31: 123-8
8. **Cassidy JT, Levinson JE and Bass JC (1986):** A study of classification criteria for diagnosis of juvenile rheumatoid arthritis. Arthritis Rheum 29: 274
9. **Hass J, Kimura A and Andreas A (1994):** Polymorphism in the upstream regulatory regions of DQA1 genes nad DRB1, QAP and DQB1 haplotypes in the German populations. Hum Immunol. 39:31
10. **Ritchie DK, Boyle J, Mcinnes J, Jansani M, Dalakas T, Grieveson P and Buchanan W (1968):** Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. J of Med. 37: 393
11. **Terasakio PL, Bernanco D, Park MS et al., (1978):** Microdroplet lympho cytotoxicity testing for HLA-A, B, C and D regions. Am J Clin Pathol. 69: 103
12. **Hafez M and El-Shennawy FA (1986)**: HLA antigens in the Egyptian populations. Forensic Science International. 31:241
13. **Buyse I, Decorte R, Baens M et al., (1993):** Rapid DNA typing of class II HLA antigens using the polymerase chain reaction and reverse dot blot hybridization. Tissue Antigen. 41:1
14. **Thonnard J, Deldime F, Heusterpreute M et al., (1995):** HLA class II genotyping: two assay systems compared. Clin Chem. 41:553
15. **Solberg OD, Mack SJ, Lancaster AK et al., (2008):** Hum. Immunol. 69: 443
16. **Fernando MM, Stevens CR, Walsh EC, De Jager PL, Goyette P, Plenge RM, Vyse TJ, Rioux JD (2008):** Defining the role of the MHC in autoimmunity: a review and pooled analysis. PLoS Genet. 4:e1000024
17. **Smollen JS, Aletaha D (2009):** Developments in the clinical understanding of rheumatoid arthritis. Arthritis Res Ther. 11:204
18. **Marta B Moroldo, Patricia Donnelly, Jocelyn Saunders, David N Glass and Edward H Giannini (1998):** Transmission Disequilibrium as a test of linkage and association between HLA Alleles and pauciarticular-onset juvenile rheumatoid arthritis. Arthritis& Rheumatism. 41:9
19. **Abdul Al-Rehiem G. Ads, Farha A, El-Chennawi, Mohammed I, Abd El Hamid,**

Mostafa A, Abo-Farrag and Azza M. Hassan (2002): "Immunogenic profile of Egyptian children with juvenile rheumatoid arthritis" The Egyptian J Immunology. 9: 33-42

20. **Pryhuber KG, Murray KJ, Donnelly P, Passo MH, Maksymowych WP, Glass DN, Giannini EH, Cobert RA (1996):** Polymorphism in the LMP2 gene influences disease susceptibility and severity in HLA-B27 associated juvenile rheumatoid arthritis. Rheumato. 23: 747-52
21. **Albert ED, Scholz S (1998):** Juvenile arthritis: genetic update. Baillieres din Rheumatol 12(2): 209-18
22. **Rundstadler JA, Säilä H, Savolainen A et al., (2003):** Analysis of MHC region genetics in Finnish patients with juvenile idiopathic arthritis: evidence for different locus specific effects in polyarticular vs. pauciarticular subsets and a shared DRB1 epitope. Genes Immun. 4: 326-35
23. **Glass DN (Feb 26, 2010):** Juvenile idiopathic arthritis and HLA class I and class II interaction and age of onset effects. Arthritis Rheum.
24. **van der Helm-van Mil AH, Verpoort KN, Breedveld FC, Huizinga TW, Toes RE, de Vries RR (2006):** The HLA-DRB1 shared epitope alleles are primarily a risk factor for anti-cyclic citrullinated peptide antibodies and are not an independent risk factor for development of rheumatoid arthritis. Arthritis Rheum. 54: 1117-1121
25. **Rumba I, Denisova A, Sochney A, Nilson B, Sangeevi CB (1997):** HLA class I genes in Latvian patients with juvenile rheumatoid arthritis. Tissue Antigens. 49: 56-60
26. **Gertsi PP, Tsakalidou KF, Spyropoulou M, Germenis A, Adam K, Taparkou A, Siamopoulou A, Drakou C, Konstantinidis T, Prieur AM, Giokas SC (1999):** Nationwide collaborative study of HLA class II associations with distinct types of juvenile chronic arthritis OCA in Greece. Eur J Immunogenet. 26(4): 299-310
27. **Turesson C, Matteson EL (2009):** Vasculitis in rheumatoid arthritis. Curr Opin Rheumatol. 21:35-40

28/02/2011