Clinical, HLA, and roentgenological follow up study of patients with juvenile arthritis: comparison between the long term outcome of transient and persistent arthritis in children

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SUMMARY Fifty two patients with juvenile chronic arthritis (JCA) and 22 patients with arthritis of short duration (transient arthritis, TA) were studied in a follow up investigation. Nineteen (37%) of the patients with JCA had peripheral arthritis or sequelae in the form of contractures at follow up, and in addition one patient was treated with corticosteroids. In contrast, only one (5%) of the 22 patients with TA had peripheral arthritis at follow up. Back pain or limitation, or both, was registered in many of the men. Sacroiliitis, verified by x ray, was often found both in JCA (39/46, 85%) and in TA (16/21, 76%). For JCA an association was confirmed with HLA-A2 and HLA-DRw8 and a negative association with HLA-DR4, and in pauciarticular JCA, in addition, a decrease of DR7. A new finding was a low prevalence of HLA-B27 in women with JCA and grade 3 or 4 sacroiliitis (2/14, 14%).

Juvenile chronic arthritis (JCA) is a heterogeneous group of disorders,^{1 2} subclassified depending on the mode of onset into pauciarticular, polyarticular, and systemic forms.

Earlier studies on JCA showed multiple associations with HLA antigens: increased prevalence of A2, Dw5, DR5, Dw8, DRw8 and decreased prevalence of DR4³, Dw2, and Dw7⁴ in JCA. Even in pauciarticular JCA increased prevalence of A2, DR5, and DRw8 and decreased prevalence of DR4 and DR7 have been found.⁵ An increased prevalence of HLA-B27 has been found in men but not women with pauciarticular disease, and is not found in patients with polyarticular disease.⁶

To fulfil the EULAR criteria⁷ patients with JCA must have had arthritis lasting for at least three months. According to the American criteria for juvenile rheumatoid arthritis,⁸ six weeks is the minimum duration. To our knowledge no study has

so far analysed possible HLA associations in a group of patients with arthritis of shorter duration than three months (designated transient arthritis (TA) in this study). The purpose of this study was to establish the outcome of inpatients with an initial presentation of arthritis and to find out whether the HLA antigens, with known associations to JCA, would differ between patients with peripheral arthritis at follow up and those without, and also to analyse the prevalence of sacroiliitis and spondylitis, especially in relation to HLA-B27.

Patients and methods

PATIENTS

The medical records of children treated for arthritis as inpatients at the Karolinska Hospital and the St Göran Hospital in Stockholm during 1950-1970 were examined. One hundred and twenty cases of aseptic arthritis were found and these individuals were contacted by letter or telephone. Eighty one patients were willing to participate in the follow up study. The EULAR criteria for juvenile chronic arthritis (JCA) were applied.⁷ Three patients who

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had arthralgia but no objective arthritis were excluded, and, additionally, four patients were excluded because of lack of adequate information in the medical records. Fifty two patients fulfilled the criteria for JCA. Of these, four patients had systemic onset with persistent intermittent fever and three of them also had rash, lymphadenopathy, or splenomegaly. Twenty two patients had had arthritis lasting less than three months and were classified as having had transient arthritis (TA). All were unrelated white Caucasians.

For the JCA group the mean age at follow up was 25 years (range 13–41) and for the TA group 26 years (range 13–41), and the mean observation time was 18 years for both JCA (range 5–35) and TA (range 5–32). Table 1 shows the mean age at onset for the different forms of JCA. For women with pauciarticular onset the debut age was <9 years in 23 cases and ≥9 years in eight cases, while for the men with pauciarticular onset the corresponding ages were 5 and 7 respectively.

Mean age at onset for the children with TA was 8 years for both male and female patients.

The patients were interviewed and the joints and the mobility of the back of each patient was investigated clinically.

LABORATORY TESTS AND HLA TYPING

Laboratory tests included a complete blood count, erythrocyte sedimentation rate Westergren, urine analysis, rheumatoid factor according to the Svartz technique,⁹ and antinuclear antibodies. The antinuclear antibodies were determined by indirect immunofluorescence using cryostat sections of rat kidneys; a titre of ≥1/25 was considered positive. Typing for HLA A, B, C, and DR was performed.^{10 11} The notation x was used for an unknown antigen. As an example, DR1, x denotes an individual who has the antigen DR1 and an unknown antigen or, alternatively, is homozygous for DR1. Seventy eight ethnically matched, normal individuals (laboratory staff) served as controls for the HLA analysis.

Table 2 Classification of x ray abnormalities in the sacroiliac joints*

Grade	Abnormality
0	Normal joints
1	Suspicious changes without specific abnormality
2	Edges not distinct Minimal sclerosis and minimal erosions Some narrowing of the joint space
3	Definite sclerosis Shaggy joint surfaces and erosive changes
4	Complete fusion or ankylosis with or without remaining sclerosis

*According to a modification of the New York criteria.¹²

ROENTGENOLOGICAL EXAMINATION

With the patients' consent and permission from the ethical committee, radiological examinations of lower thoracic and lumbar spine were performed. The sacroiliac joints were x rayed using two projections: one from the anteroposterior view of the pelvis with the subject supine, the x ray tube angled 25 degrees caudocephalad, and one with the patient in the prone position without angulation of the tube. Both projections included both sacroiliac joints. As controls we used a series of consecutive x ray investigations of the back of patients in hospital, whose working capacity was being investigated or who were inpatients for rehabilitation purpose: 93 men aged 20–63 and 128 women aged 26–65; most being between 45 and 55 years of age. Some of them had backache due to spondyloarthritis. We were not able to exclude previously undiagnosed clinical sacroiliitis. The changes in the sacroiliac joints were classified according to a modified version of the New York criteria¹² (Table 2). The radiographs were evaluated on two different occasions by the same radiologist (NL); on the second assessment the radiologist had no knowledge of the findings of the first evaluation. Grades ≥2 were scored as signs of sacroiliitis. The sacroiliac joints on either side were graded separately. In a few cases where the gradings

Table 1 Mean onset age in years, juvenile chronic arthritis (JCA)

	M/F (No)	Onset age (years)		
		Men	Women	Total
Pauciarticular	12/31	8	6	6
Polyarticular	1/4	13	5	6
Systemic	3/1	6	5	6
All JCA		8	6	6

Table 3 Patients with back pain or limitation, or both

	JCA*		TA*	
	Men (n=16)	Women (n=36)	Men (n=11)	Women (n=11)
Back pain	5	0	2	0
Limitation	5	6	1	4
Limitation and back pain	0	2	1	1
No evaluation	1	4	1	1

*JCA=juvenile chronic arthritis; TA=transient arthritis.

for the right and left joint differed the highest grade was scored. A complete *x* ray examination of the hips was performed in three individuals. Clinical, laboratory, and radiographic examinations were all performed separately without knowledge of the results of the other investigations or of HLA determination.

STATISTICAL METHODS

Statistical analysis was performed by Fisher's exact test. In cases where no a priori hypothesis had been formulated the *p* values were corrected (*p_c*) by multiplying them by the number of tests made and, secondly, Fisher's two sided test was used. The following comparisons performed in this investigation were subject to an a priori hypothesis based on results published earlier³⁻⁵: increased prevalence of A2, DR5, DRw8, low prevalence of DR4 and DR7. In these instances a one sided Fisher's test was used.

Results

CLINICAL MANIFESTATIONS AT FOLLOW UP Arthritis

Nineteen patients (37%) in the JCA group (seven men, 12 women) had signs of arthritis or sequelae in the form of contractures at the clinical follow up examination. Of these, two men and seven women (one with bilateral prosthesis) had clinical signs of hip joint involvement. In addition, one man with systemic onset JCA was receiving treatment with corticosteroids. One man in the TA group had moderate restriction of abduction in the right hip, but the remaining patients were free of arthritis at follow up.

Back pain or limitation, or both

Table 3 gives details of patients with back pain or limitation, or both.

Eye manifestations

Thirteen (25%) (seven men, six women) patients in

Table 5 *x* Ray abnormalities of the sacroiliac joints in JCA* and TA*

<i>x</i> Ray changes	JCA (n=52)		TA (n=22)		Controls (n=221)	
	Men (n=16)	Women (n=36)	Men (n=11)	Women (n=11)	Men (n=93)	Women (n=128)
0	1	4	1	2	70	76
1	2	0	1	1	8	23
2	5	12	6	4		
3	6	12	3	3	15	29
4	2	2	0	0		
ND*	0	6	0	1	0	0

*JCA=juvenile chronic arthritis; TA=transient arthritis; ND=not done.

the JCA group, but none in the TA group, had a history of acute or chronic uveitis.

Psoriasis

Three cases of psoriasis were found in the JCA group and one in the TA group.

Laboratory data

At the follow up examination the erythrocyte sedimentation rate was >20 mm/h in four women and >15 mm/h in two men with JCA, but it was normal in all patients with TA. Seven of the women in the JCA group had positive antinuclear antibodies of low titre. None of the men in the JCA group and none in the TA group, however, were positive for antinuclear antibodies. Only two women with positive antinuclear antibodies had arthritis or signs of arthritis at follow up. A positive rheumatoid factor test was recorded in one case (a 33 year old woman with TA) at follow up.

Functional class

Table 4 shows the functional class¹³ at the time of the follow up of the patients with JCA and TA.

RADIOGRAPHIC FINDINGS

Table 5 presents the results of *x* ray investigations of the sacroiliac joints. The prevalence of sacroiliitis in JCA was 85% (39/46), in TA 76% (16/21), and in controls 20% (44/221). Five men and 15 women were <20 years of age at follow up. Of these, three men and seven women had grade 1 or 2 sacroiliitis. In these 10 patients the evaluation of the radiographs was difficult as during growth the radiographic outline of the cortical margins of the joints is normally ill defined.¹⁴

Twenty two of 46 patients with JCA (48%) and 6/21 (29%) of patients with TA had sacroiliitis grade ≥ 3 . Three of the seven (43%) men with JCA and arthritis at follow up had sacroiliitis grade ≥ 3 .

Table 4 Functional class according to Steinbrocker¹³

Functional class	JCA* (n=52)			TA* (n=22)	Total (n=74)
	Pauci (n=43)	Poly (n=5)	Systemic (n=4)		
I	26	1	3	17	47
II	14	1	0	4	19
III	0	3	1	0	4
IV	2	0	0	1†	3
ND*	1	0	0	0	1

*JCA=juvenile chronic arthritis; TA=transient arthritis; ND=not done.
†Neurological disease.

whereas of the nine men who had no arthritis at follow up, five (56%) had sacroiliitis grade ≥ 3 . For girls with JCA the corresponding figures were 5/11 (45%) and 9/19 (47%) respectively. Of the 10 men with JCA and back pain or stiffness, or both, seven had sacroiliitis grade ≥ 3 ; of the eight women with JCA and back pain or stiffness, or both, two had sacroiliitis grade ≥ 3 (two were not x rayed). In three patients, who had bilateral sacroiliitis grade 3, spondylitis was found.

RESULT OF THE TISSUE TYPING

Tables 6, 7, and 8 present the results of HLA-A, B, C, and DR antigen determinations for all patients with JCA, for pauciarticular JCA, and for TA.

There was no deviation for HLA-B27 in patients with peripheral arthritis at follow up. Seven of the 10 men with JCA who had back pain or limitation, or both, at follow up were B27 positive, while all the eight women were B27 negative.

In patients with sacroiliitis 7/13 men and 5/26 women were HLA-B27 positive. When only grade 3 or 4 sacroiliitis was considered we found that only 2/14 women (14%) were HLA-B27 positive, whereas this antigen was found in 6/8 men (75%) (Fisher's two sided test, $p < 0.01$); p_c values were not significant.

The cases with spondylitis included two HLA-B27 negative women and one HLA-B27 positive man. None of them had psoriasis, colitis, or Crohn's disease.

Of women in the JCA group with pauciarticular

Table 7 Prevalence (%) of selected HLA-A, B, C, and DR antigens in patients with juvenile chronic arthritis of pauciarticular onset compared with controls

HLA	Patients			Controls (n=78)
	Men (n=12)	Women (n=31)	All (n=43)	
A2	75	81**	79**	54
A3	17	13†	14††	38
B27	33	10	16	10
Cw1	0	0	0†	12
DR1	8	16	14	10
DR2	0†	16	12††	33
DR3	42†	26	30	19
DR4	8*	10**	9***	37
DR5	8	13	12	10
DRw6	0	7	5	10
DR7	8	3**	5**	28
DRw8	42**	45***	44***	9

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; all Fisher's one sided test.

† $p < 0.05$; †† $p < 0.01$; both Fisher's two sided test.

onset and arthritis or sequelae of arthritis at follow up, only 1/8 (13%) had HLA-DRw8 compared with 13/23 (57%) with pauciarticular onset who were free of arthritis and sequelae of arthritis at follow up; the uncorrected p value was significant (Fisher's two sided test, $p < 0.05$), but not the corrected p value. Of the eight women with pauciarticular onset and arthritis or sequelae at follow up, four had polyarticular disease at the time of the follow up examination and the HLA-DR phenotypes of these patients were: 1,x; 2,5; 5,w8; and 7,x. The remaining four still had pauciarticular disease and their HLA-DR phenotypes were 2,x; 1,x; 3,4; and 4,5.

Table 6 Prevalence (%) of selected HLA-A, B, C, and DR antigens in patients with juvenile chronic arthritis compared with controls

HLA	Patients			Controls (n=78)
	Men (n=16)	Women (n=36)	All (n=52)	
A2	75	75*	75*	54
A28	6	6	6†	21
B12	6	14	12†	29
B27	44††	14	23†	10
Cw2	25†	8	13	6
DR1	19	14	15	10
DR2	0††	14†	10††	33
DR3	25	31	31	19
DR4	13*	11**	12***	37
DR5	13	11	12	10
DRw6	0	6	4	10
DR7	13	3†††	6†††	28
DRw8	31*	47***	40***	9

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; all Fisher's one sided test.

† $p < 0.05$; †† $p < 0.01$; ††† $p < 0.001$; all Fisher's two sided test.

Table 8 Prevalence (%) of selected HLA-A, B, C, and DR antigens in patients with transient arthritis compared with controls

HLA	Patients			Controls (n=78)
	Men (n=11)	Women (n=11)	All (n=22)	
A2	82	36	61	54
B27	17	9	13	10
DR1	8	18	13	10
DR2	0†	55	26	33
DR3	17	27	22	19
DR4	27	27	30	37
DR5	0	0	0	10
DRw6	0	0	0	10
DR7	0	0	0††	28
DRw8	0	9	4	9

† $p < 0.05$; †† $p < 0.01$; both Fisher's two sided test.

Discussion

Even though it is impossible to give a reliable prognosis for an individual patient with JCA, the overall prognosis is favourable. Edström in 1958 noted that 62% of 85 patients recovered without defects,¹⁵ and more recently Ansell reported similar figures.¹ Also in the present study most of the patients with JCA (32/52, 62%) were without peripheral arthritis or sequelae of peripheral arthritis at the clinical follow up examination. Those with TA had an even better outcome; apart from one, all were free of peripheral arthritis at follow up.

In both JCA and TA a surprisingly high prevalence of sacroiliitis was found. In the group with JCA 39/46 (85%) had x ray evidence of sacroiliitis, and three also had spondylitis.

The sacroiliac joint is one of the most challenging articulations for the radiologist.¹⁴ Owing to this or owing to differences in patients or differences in follow up times elapsed before x ray examination, varying prevalences of sacroiliitis in JCA have been found by different workers: Carter found 24%,¹⁶ Jeremy and coworkers 43%,¹⁷ Veys *et al* 55%,¹⁸ and Arnett *et al* 28%.¹⁹ In a clinical study from northern Sweden, which has a high prevalence of HLA-B27 in the population,²⁰ Rantapää Dahlqvist *et al* observed that in 28 patients with classical adult onset rheumatoid arthritis, selected to be HLA-B27 positive, 82% had radiographic evidence of sacroiliitis, whereas among 28 HLA-B27 negative controls with rheumatoid arthritis, 57% had sacroiliitis; the overall prevalence being 70%.²¹

The high prevalence of sacroiliitis in our study may be partly explained by the fact that we chose to take even grade 2 as evidence of radiographic sacroiliitis. This is in accordance with Rantapää Dahlqvist *et al*²¹ but in contrast with Arnett *et al*,¹⁹ who only included grades 3–4. Jeremy *et al* studied patients with 'definite' sacroiliitis described as follows: blurring or sclerosis of joint margins, juxta-articular erosions, or joint fusion.¹⁷

Of the patients with JCA with grades 3 or 4 sacroiliitis in our study, 8/22 (36%) were positive for HLA-B27, which is a low prevalence compared with the findings of Veys and coworkers¹⁸ and Arnett *et al*,¹⁹ who found that among patients with JCA with grade 3 and 4 sacroiliitis, 95% and 93% respectively were HLA-B27 positive.

In a 10 year follow up study of sacroiliitis in JCA Hall *et al* found that 9/66 (14%) patients had sacroiliitis of the ankylosing spondylitis type.²² All were HLA-B27 positive, all presented pauciartthritis, and seven were men. Additionally, they noted sacroiliac changes, interpreted as secondary to hip involvement, in seven patients, of whom six were

women and only one, a woman, was B27 positive. In our study only a few patients had their hip joints x rayed at follow up.

Even in the controls, who were older patients in hospital, the prevalence of sacroiliitis was high (20%). There are only a few investigations of the prevalence of sacroiliitis among healthy persons. Cohen *et al* found erosion of the sacroiliac joint, subarticular sclerosis, or both, in approximately 6% of normal subjects under the age of 50 and in 24% of those over the age of 50.²³

The finding of multiple associations with HLA antigens confirms and extends earlier reports.^{3–5} In the patients with JCA and in those with pauciarticular onset JCA we found a high prevalence of A2, DRw8, and a low prevalence of DR4. In patients with JCA with pauciarticular onset a low prevalence of DR7 was found, confirming the findings of Hall *et al*.⁵ Men with JCA and grade 3 or 4 sacroiliitis had a slightly higher prevalence of HLA-B27 than women. A low prevalence of DR2 was found in patients with JCA and in those with pauciarticular onset of JCA, in accordance with the findings of Morling *et al*.⁴

In women with JCA and pauciarticular onset the prevalence of HLA-DRw8 was higher among those without peripheral arthritis than in patients who had peripheral arthritis at follow up. If this finding is confirmed it could mean that DRw8 is a favourable prognostic sign in this subgroup of patients. In the group with TA the prevalence of DRw8 was normal and, with the reservation that only a small number of patients with TA was investigated, this finding could imply that the minimum duration of arthritis of three months used to defined JCA is relevant.

Most of our patients lived a normal life and did not have contact with the medical service. Dequeker and Mardjuadi used a different approach.²⁴ They studied patients with JCA still attending an adult rheumatology or orthopaedic clinic, and the characteristics of their group of patients differed in some respects from ours. The majority had a later onset than most patients in our study; the mean age at onset in their group of patients was 10.4 years and that in our 6 years. Whereas only 12% (6/51) of our patients were in functional class III or IV, the corresponding figure in their patients was 25%.

Previous authors have noted that children with polyarticular onset have the worst prognosis.^{1, 25} Although our group of patients with polyarticular onset was small, it was interesting that three of the five children were in functional class III. In contrast the outcome in the children with pauciarticular or systemic onset was excellent, with only three of the 46 being in functional class III or IV.

When the p values were multiplied by the number of comparisons the corrected p value (p_c) obtained

for the new findings in this study lost statistical significance. Future studies might elucidate further the correlation between HLA and prognosis of JCA.

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