Progression of articular and extraarticular damage in oligoarticular juvenile idiopathic arthritis

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Abstract

Objective

Evaluate damage in oligoarticular JIA, estimating its frequency, risks and probability over time.

Methods

A cross-sectional and retrospective analysis of Juvenile Arthritis Damage Index (JADI) scoring, with both articular and extraarticular components, active joint count, disability index by CHAQ and Steinbrocker class, physician's global assessment, child's pain and overall well-being visual analogue scale (VAS), was conducted in patients with oligoarticular JIA. Damage risk factors were estimated by univariate analysis and by generalised linear model. The probability of damage over time was estimated by survival analysis and damage progression rates were calculated by hazard function.

Results

Seventy-five JIA cases were assessed, 89.3% persistent and 10.7% extended oligoarthritis, with median follow-up duration 1.7 years (IQR 1.3–3.1). Damage occurred in 38.7%. JADI-A correlated moderately only with the number of limited joints (r_s= 0.50, p<0.0001). Female sex (OR 3.5, 95% CI 1.0–11.6), DMARD use (OR 3.9, 95%CI 1.0–15.0) and knee involvement (OR 4.2, 95%CI 1.3–13.5) were significantly associated with joint damage, whereas only joint steroid injection was associated with extraarticular damage (OR 5.9, 95% CI 1.8–19.3). Damage probability at 5 years was 50% for JADI-A, and 57% for JADI-E. Calculated hazard rates each year were 16.1% and 16.3%, for JADI-A and JADI-E, respectively.</p>

Conclusion

Sex, DMARD use and knee involvement were associated with joint damage, whereas only joint steroid injection was associated with extraarticular damage, which progressed at stable rates over ten years.

Key words

damage, disability, juvenile idiopathic arthritis, oligoarthritis, outcome

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Introduction

Juvenile idiopathic arthritis (JIA) impacts physical function, psychosocial development and quality of life. It may cause disability and growth impairment (1). JIA is a heterogeneous disease; its long term outcome is also variable, depending on disease presentation and course (1, 2). Oligoarticular JIA is the most prevalent subtype, especially in western countries, where it represents 27 to 56% of all JIA cases (3-5). Outcome studies to date have described damage frequency and damage risk, but to our knowledge, studies specifically addressing the oligoarticular subtype are scarce (6, 7). It seems to present better outcome compared to other JIA subtypes (8), but 35% of patients still enter into adulthood with persistent active disease (9), 40% of those evolving to extended oligoarthritis eventually present severe physical disability (10), and up to 70% of those with oligoarthritis also affected by uveitis present ocular damage during long term follow-up (11), although more recent studies have demonstrated improved visual outcome (12).

Damage accrual is also an important concern and a quantitative tool to rate the extent of damage in JIA, the Juvenile Arthritis Damage Index (JADI) (13), was recently developed and validated. The concept of damage is defined by persistent changes in anatomy, physiology, pathology process or function, as result of prior disease activity, therapy complications, or co-morbid conditions, but not due to current active arthritis, and that should be present for at least 6 months, despite previous therapy, including exercise and rehabilitation.

JADI tool has two components: the JADI-A scores joint damage and JADI-E extraarticular damage. It has been used for assessing different JIA sub-types in several recent studies (13-17) and revalidated in a large cohort with long term follow-up (15). The JADI tool can be easily scored by clinical history revision, standardised joint assessment and routine procedures, such as radio-graphs or ophthalmological exams. It has been shown to be reliable and feasible in different studies addressing all

subtypes, excluding enthesitis related arthritis (13-15), only systemic JIA (16) and enthesitis related arthritis (17). Therefore, this study aimed to quantify damage using the JADI tool in a series of oligoarticular JIA, estimating its frequency, risks and progress over time.

Patients and methods

Patient selection

A combined cross-sectional and retrospective assessment was conducted in consecutive patients attended at a pediatric rheumatology clinic, between January 2007 and August 2008. The inclusion criteria were: JIA diagnosis and classification according to the 2001 International League of Associations for Rheumatology (ILAR) revised criteria (18), which is based on clinical and laboratory findings observed during the first six months of clinical course and characterised primarily by the presence of persistent arthritis for at least six weeks in patients up to 16 years of age. Individuals with fewer than five joints involved during the first six months after onset were selected and those who were attended for the first time between 1996 and 2008, who maintained a regular follow-up schedule, with at least six months of disease duration, and whose parents or guardians signed the term of free informed consent were included. Exclusion criteria were other JIA subtypes or associated disease diagnoses. The study protocol was approved by the Institutional Ethics Committee.

Study design

The study consisted of a cross-sectional assessment during the final consultation and a retrospective review of the case notes conducted from the first to the last appointment. Retrospective data collection included a comprehensive revision of all appointments for clinical data, radiographs, ophthalmological assessment and treatment in a standardised case report form.

Clinical and joint assessment

The clinical assessment during the final consultation comprised: 1) general physical exam; 2) 75-joints assessment for swelling, pain on motion, limited range of motion, and the number of

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active joints (defined by the presence of swelling or, when absent, the limited range of motion accompanied by either pain or tenderness on motion); 3) oligoarticular JIA course (persistent or extended); 4) physician's global assessment of disease activity by 10 cm visual analog scale (VAS), where 0 =no activity and 10 = maximum activity; 5) Steinbrocker functional class (19); 6) current disease activity status according to Wallace et al. (20), defined by the absence of active arthritis, physician's global assessment indicating no disease activity, absence of systemic symptoms, absence of active uveitis and normal erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP); 7) articular and extraarticular damage assessment by JADI tool (13). JADI-A was scored in each of the 36 joints nominated in the tool glossary as follows: 0 = no damage; 1 = partialdamage (presence of limited range of motion, flexion contracture or valgus deformity); 2 = severe damage (presence of ankylosis or prosthesis), where the maximum score possible is 72. The JADI-E includes 13 items scoring 5 domains: ocular, musculoskeletal excluding joints, cutaneous, endocrine and any organ/system secondary amyloidosis. Each item is scored 1 or 0, for damage presence or absence, except uveitis complications, which are scored from 0 to 3, according to severity of damage. Cataract and/or vision loss is scored 1, eve surgery is scored 2 and legal blindness is scored 3. JADI-E maximum score is 17. All clinical assessments, the cross-sectional and retrospective review, were performed by the same assessor (JOS) throughout the study.

During the cross-sectional assessment, the parents were asked to complete: 1) a 10 cm VAS rating child's overall well-being (0 = very good and 10 = very poor); 2) a 10 cm VAS rating child's pain (0 = no pain and 10 = very severe pain); 3) physical function by CHAQ disability index (DI) (21), categorised in: 0 = no disability, >0 and ≤ 0.5 = mild disability, >0.5 and ≤ 1.5 = moderate disability, and >1.5 = severe disability (22). During the study consultation, clinical and demographic data were retrospectively compiled from the case-notes and added to the case-report form listing: sex, current age, disease onset age, presence of antinuclear antibodies (ANA), rheumatoid factor (RF) and HLA-B27 typing, dates of first and last appointments, disease duration, time interval between symptoms onset and diagnosis, Tanner puberty assessment and previous therapy.

Statistical analysis

Descriptive statistics is presented as median and interquartile range (IQR) for continuous variables and percentual frequency for categorical variables. The Spearman correlation test was performed for associations between JADI-A and JADI-E respective scores and the following variables: JADI-E and JADI-A scores; age at JIA onset; CHAQ-DI; physician's global assessment (10 cm VAS), pain and child's overall well-being (10 cm VAS); time interval between symptoms onset and diagnosis (years); follow-up and disease duration (years); number of swollen, limited, painful and active joints. Spearman's rank correlation coefficients $(r_c) < 0.4$ were considered low, $0.4 \le r_{c} < 0.7$ moderate, and $r_{s} \geq 0.7$ high.

Univariate analysis was performed to identify clinical variables that can predict either articular and extraarticular damage, testing the following variables: sex, positive ANA, previous therapy with either non-steroidal antiinflammatory drugs (NSAIDs), oral steroids, disease-modifying anti-rheumatic drugs (DMARDs), joint steroid injections, JIA course, current disease activity status, Steinbrocker functional class and arthritis involvement in each of the joints or joint group. The selected clinical variables were based on the concept that besides baseline characteristics and disease process itself, treatment can also influence damage. This was followed by a generalised linear model adjustment, considering damage as the outcome variable, with binomial distribution and logistic link function, with the previously listed variables and continuous variables as current age, disease onset age, physician's global assessment VAS, pain and child's overall well-being VAS, time from symptoms to diagnosis, time of follow-up and

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disease duration, number of swollen, limited, painful and active joints. The results are presented as odds ratio (OR) with 95% confidence interval (CI).

Survival analysis was performed using the actuarial method, estimating the probability of articular and extraarticular damage. Patients presenting no damage were censored at 1-year intervals. Complementary values (1-p) were used to calculate the probability of damage, where p was the probability of damage absence at a given time. The instantaneous rates of both articular and extraarticular damage events were calculated by hazard function at each year interval during the entire follow-up.

For all statistical tests, significance was established at 5% with correspondent two-sided *p*-value, using SAS for Windows, version 9.1.3.

Results

Subjects

Eighty patients with oligoarticular onset JIA were invited and agreed to participate in the cross-sectional assessment. No selection was performed, apart from the opportunity of clinical attendance and time availability of the dedicated examiner. Of those, five were excluded, 3 with Down syndrome and 2 with less than 6 months disease duration; therefore, data from 75 patients were analysed. Demographic and clinical features are shown in Table I. Median onset age was 7.1 years (IQR 3.6-9.2), median disease duration was 2.7 years (IQR 1.8-5.2) and median follow-up duration was 1.7 years (IQR 1.3–3.1). At the time of the cross-sectional assessment, 67 (89.3%) cases presented persistent and 8 (10.7%) extended oligoarticular JIA. Forty-eight (64.0%) patients had active disease, 73 (97%) were treated with NSAIDs, 5 (6.7%) with prednisone, 39 (52%) received one or more joint steroid injections (triamcinolone hexacetonide), 19 (25.3%) received DMARDs and none of them received biological treatment. For those under DMARD therapy, 18 received methotrexate, 2 sulfasalazine, 1 leflunomide and 1 cyclosporine A. Two patients received two or more DMARDs over time.

ANA was tested by indirect immunofluorescence using HEp-2 cells and tit-

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 Table I. Demographic and clinical features

 of 75 oligoarticular JIA cases.

	n	(%)	
Sex			
Female	42	(56.0)	
Male	33	(44.0)	
F:M	1.3:1		
ILAR Category ⁹			
Persistent oligoarthritis	67	(89.3)	
Extended oligoarthritis	8	(10.7)	
Disease activity			
Active	48	(64.0)	
Inactive	27	(36.0)	
ANA positive [†]	38	(52.8)	
NSAID treatment [‡]	73	(97.3)	
Prednisone treatment	5	(6.7)	
Intraarticular corticosteroid	39	(52.0)	
DMARD treatment§	19	(25.3)	
	Median (IQR)		
Swollen joint count	2	(0-4)	
Painful joint count	0	(0-0)	
Limited joint count	0	(00)	
Active joint count	2	(0-4)	
Age at disease onset, years	7.1	(3.6–9.2)	
Age at study visit, years	11.6	(8.9–13.8)	
Time from symptoms onset to	0.5	(0.3–1.6)	
diagnosis, years		(1 2 2 1)	
Follow-up duration, years	1.7	(1.3-3.1)	
Disease duration, years	2.7	(1.8–5.2)	

⁹ILAR: International League of Associations for Rheumatology; ^{*}NSAID: non-steroidal anti-inflammatory drugs; ^{*}DMARD: disease-modifying anti-rheumatic drugs; ^{*}ANA: anti-nuclear antibodies; 72 were tested.

ers >1:40 were positive. Considering all tested (n=72), positive ANA was recorded in 52.8% (n=38), with the following titers: 1:40 (6), 1:80 (17), 1:160 (11), and 1:320 (4). Rheumatoid factor was tested in 68 patients, all were negative by the latex test. HLA-B27 was tested in 11 patients, all negative.

Retrospective review

All previous clinical appointments were retrospectively examined by the same assessor (JOS), a fully trained specialist. There were 871 appointments registered in the 75 patients medical records, with a median of 9.0 visits each, (IQR 7–15), all from 1996 to 2008. All patients had scheduled consultations for uveitis screening by the same ophthalmologist. During follow-up, 156 joint steroid injections were performed in 39 patients, with a median of four (IQR 0–4) each patient. Eleven patients underwent more than one injection in the same joint over time.

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Fig. 1. Description and frequency of scored joints by JADI-A (**1-a**) and extraarticular scored items by JADI-E (**1-b**), in 75 patients followed over 0.3 to 9.9 years. MTF: metatarsophalangeal; PIP: proximal interphalangeal; TMJ: temporomandibular joint.

Joint damage

Twenty-nine patients (38.7%) scored JADI-A >0 in at least one joint. The median JADI-A score was 0, (IQR 0-2). The most frequently scored joints were the knees and metatarsophalangeal joints (Fig. 1-a). Most patients presented bilateral damage in symmetrical joints. Eighteen cases scored knee damage, with flexion contracture $<25^{\circ}$ in 10; and of those, 7 were bilateral; knee valgus deviation occurred in 8 cases and it was bilateral in 7. Metatarsophalangeal joint damage due to foot arch flattening, as result of previous arthritis, was observed in 9 cases and it was bilateral in 8. One patient presented hind feet valgus deformity and one patient presented temporomandibular joint (TMJ) damage with severe asymmetric mandibular growth and mouth opening restriction. Four scored simultaneous damage in two or more joints: knee damage associated with the third PIP flexion contracture (2), feet arch flattening and elbow flexion contracture (1), and knees valgus deviation and flattened feet arches (1). No damage was observed in the cervical spine, shoulder, wrist, metacarpophalangeal and hip joints in any of the cases.

Extraarticular damage

Twenty-nine cases (38.7%) scored JADI-E >0. The median JADI-E score was 0, (IOR 0-1). Short stature, which was attributed to disease activity, was observed in 2 patients. Leg-length discrepancy was the most frequently scored item, in 22.7%. Six (8.0%) presented periarticular subcutaneous atrophy due to steroid injection and three (4.0%)showed thigh muscle atrophy (Fig. 1b). Five patients (6.7%), all with persistent oligoarticular JIA course, though only one with positive ANA, presented uveitis damage accrual, diagnosed by ophthalmologist during routine surveillance. All developed cataracts, which was bilateral in 3. Two underwent surgery; of those, one had eye enucleation. Three (4%) presented unilateral visual loss.

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Table II. Correlation between JADI-A and JADI-E scores and disease variables by Spearman's coefficient.

Variables	Number of patients	JADI-A score	JADI-E score
JADI-E score	75	0.15	_
Age at disease onset	75	-0.12	-0.22
CHAQ-DI [†]	75	0.07	0.01
Pain VAS [‡]	73	-0.03	-0.03
Parent's VAS [‡]	73	-0.02	0.11
PGA§	74	0.26*	0.01
Time to diagnosis	75	0.08	0.08
Follow-up duration	75	-0.07	0.06
Disease duration	75	-0.03	0.02
Active joints	75	0.30*	0.01
Swollen joints	75	0.30*	0.01
Limited joints	75	0.50*	0.25*
Painful joints	75	0.12	-0.16

[†]CHAQ-DI: Childhood Health Assessment Questionnaire Disability Index; [‡]VAS: 10 cm visual analogue scale; [§]Physician's global assessment by 10 cm visual analogue scale. ^{*}*p*<0.05.

Table III. Variables significantly associated with the presence of damage by generalised linear model.

Variable	Odds ratio (OR)	95% Confidence interval	Standard error	<i>p</i> -value
JADI-A				
Sex (Female vs. Male)	3.5	1.0 - 11.6	2.1	0.04
DMARD treatment †	3.9	1.0 - 15.0	2.7	0.05
Knee arthritis	4.2	1.3 - 13.5	2.5	0.02
JADI-E				
Joint steroid injection	5.9	1.8 - 19.3	3.6	0.004

The OR was obtained considering absence of damage as baseline.

Osteoporosis, avascular necrosis, striae rubrae, pubertal delay, diabetes mellitus or amyloidosis were not observed in any of the cases. Considering both articular and extraarticular damage, no damage was scored in only 31 (41%)

Functional ability

patients.

In the cross-sectional assessment, moderate to severe disability was observed in 21.3%, mild disability in 22.7% and no disability in 56%, according to CHAQ-DI. Seven patients (9.3%) were classified as Steinbrocker class II, while the remaining presented no disability according to the Steinbrocker classification (90.7%). Child's pain and global assessment of overall wellbeing by parents and physician's global assessment (10 cm VAS) median (IQR) values were 1.7 (IQR 0.1–4.1), 0.3 (IQR 0.1–2.4) and 1.0 (IQR 0.1–2.0), respectively. Spearman's correlation analysis

Correlations of disease variables with JADI-A and JADI-E scores were all low, except for the number of joints with limited range of motion and JADI-A (r_s =0.50, *p*<0.0001), which was moderate (Table II).

Risk factors associated with damage

Univariate analysis resulted in the following significant risk factors associated with joint damage: Steinbrocker functional class II (OR 31.0, 95%CI 1.7–555.6; p=0.0005) and knee involvement (OR 2.7; 95%CI 1.0–7.0; p=0.04). Only joint steroid injection was significantly associated with extraarticular damage (OR 4.0; 95%CI 1.5–11.2; p=0.01). A generalised linear model was constructed, considering damage as outcome variable. Female sex (OR 3.5, 95%CI 1.0–11.6), DMARD use (OR 3.9,95%CI 1.0–15.0) and knee involvement (OR 4.2, 95%CI PAEDIATRIC RHEUMATOLOGY

1.3–13.5) were associated with joint damage, whereas only joint steroid injection was associated with extraarticular damage (OR 5.9, 95%CI 1.8–19.3), in the final model (Table III).

Damage probability

Actuarial survival curves with yearly censoring interval for articular and extraarticular damage are presented in Figure 2a and 2b, respectively. The Y-axis represents the damage-free probability (p); therefore, damage probability is represented by complementary value (1-p). Damage probability increased over time, reaching 50% for articular and 57% for extraarticular damage after 5 years.

Damage hazard function

The calculated mean hazard rates, at each year interval, were 16.1% for JADI-A and 16.3% for JADI-E, with similar risk proportion each year, up to 9.9 years.

Discussion

A series of oligoarticular JIA cases with median disease duration of 2.7 years and median follow-up duration of 1.7 years was evaluated to estimate quantitative damage according to the JADI tool. Both, JADI-A and JADI-E damage scores of at least 1 were identified in 38.7% of cases. The frequency was comparable to that obtained in the validation study including different JIA subtypes, which was 47% and 37% for JADI-A and JADI-E, respectively (13). A recent study using the same tool, but addressing distinct JIA subtypes, indicated joint damage of 60.7% and extraarticular damage of 39.3% (14). Another study, addressing systemic JIA, resulted in 38% for joint damage and 19% for extraarticular damage (16). Enthesitis related arthritis (ERA) assessment was recently published (17), with joint damage reported in 34.7% and extraarticular damage in 10.2% of cases. In one of the largest series reported to date, investigating long-term outcome in different JIA subtypes, but excluding ERA, joint damage frequency was 34.2% and extraarticular damage was 26.1% (15). In all the previously referred studies a minimum

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5 years median disease duration was reported, however follow-up duration was not specified (13-17).

To our knowledge, no particular analysis of damage in oligoarticular JIA has been published. Oligoarticular JIA subtype was chosen due to its higher prevalence (3, 5, 23). This allowed estimating frequency of damage in oligoarticular JIA subtype. Apart from the JIA subtype selection and the opportunity of clinical attendance, this study was conducted without any other selection. No limit for disease duration was established, which was permitted in order to estimate damage during early disease course as well. A diagnostic delay of more than 1 year was observed in 34.7% of the patients; however, this could be changing over time, since the median gap between symptom onset and diagnosis was five months.

The proportion of patients with short stature, which scored JADI-E growth failure (2.7%), was lower compared to previous studies by Viola *et al.* (11%) (13), Russo & Katsicas (13%) (16) and Sarma *et al.* (39.3%) (14). This difference could be explained by the proportion of cases with less severe disease among the patients studied here.

Concerning the pattern of joint damage, the knees were most frequently scored, in 24% of cases, followed by metatarsophalangeal joints, in 12%. The proportion of metatarsophalangeal damage was similar to that reported by Solari et al. (15), indicating that damage in this joint may be more frequent. For JADI-A scoring, all the metatarsophalangeal joints are considered as a single unit, and this was represented mainly by foot arch flattening. One report of oligoarticular JIA has been published indicating isolated small joint involvement at presentation (24), but to our knowledge, persistent arthritis or small joints damage have not been reported. Temporomandibular joint (TMJ) damage was observed in only one patient, but resulted in severe micrognathia, retrognathia and limited mouth opening. Ocular damage and unilateral visual loss rates were 6.7% and 4%, respectively; these rates were lower compared to a report by Marvillet et al. (25). Ocular complications and visual loss rate in re-



Fig. 2. Survival curves for damage scoring over time (2-a JADI-A, 2-b JADI-E). The x-axis shows disease duration in years. The y-axis shows the proportion of patients without damage. Dotted and dashed lines represent the lower and upper limits for the 95% confidence interval, respectively.

cent JIA studies varied from 34 to 37% and 5.6 to 11.7%, respectively (12, 26, 27), meaning that ocular damage is still of major concern in oligoarticular JIA. Female sex, knee involvement and DMARD treatment were associated with joint damage. Female sex is regarded as a poor outcome predictor (28-30), and as a uveitis risk (31). DMARD use may indicate more severe disease and was also shown to be a joint damage predictor in systemic arthritis (32). Extraarticular damage was associated only with joint steroid injection, reflecting subcutaneous atrophy, which was described in 8% of cases and 3.8% of treated joints. A recent review refers to cutaneous atrophy in 2.3 to 8.3% of treated patients (33).

Damage progress was retrospectively examined in the present series and risk rates did not vary over time up to 10 years, suggesting that a period of greater or lesser risk for damage does not exist. Even for those individuals who did not develop damage after several years, the risk is never null. Early diagnosis and early treatment are considered critical factors for damage accrual in polyarticular JIA (34).

Although the majority of our patients did not present functional impairment, 44% still showed mild to moderate disability, assessed by CHAQ-DI. It has to be considered that 64% presented active disease during the cross-sectional assessment. Unlike others, who have found moderate to high (13, 14,

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16, 17) correlations between JADI-A scores and CHAQ disability index, in the present study the correlation was low, possibly indicating lower correlation between CHAQ and joint damage scores in less severe JIA.

The limitations of this study are the small sample size from a single centre and limited follow-up duration. In spite of these limitations, the JADI-A component confirmed its measurement properties in oligoarticular JIA. In practice, damage progress and damage risk assessment is valuable for achieving recommended treatment during the window of opportunity in the early disease stages.

References

- 1. MOORTHY LN, PETERSON MGE, HASSETT AL, LEHMAN TJA: Burden of childhood-onset arthritis. *Pediatr Rheumatol Online* 2010; 8: 20.
- ALBERS HM, BRINKMAN DM, KAMPHUIS SS et al.: Clinical course and prognostic value of disease activity in the first two years in different subtypes of juvenile idiopathic arthritis. Arthritis Care Res 2010; 62: 204-12.
- 3. RAVELLI A, MARTINI A: Juvenile idiopathic arthritis. *Lancet* 2007; 369: 767-78.
- SOLAU-GERVAIS E, ROBIN C, GAMBERT C et al.: Prevalence and distribution of juvenile idiopathic arthritis in a region of Western France. Joint Bone Spine 2010; 77: 47-9.
- QUARTIER P: Current treatments for juvenile idiopathic arthritis. *Joint Bone Spine* 2010; 77: 511-6.
- GUILLAUME S, PRIEUR AM, COSTE J, JOB-DESLANDRE C: Long term outcome and prognosis in oligoarticular-onset juvenile idiopathic arthritis. *Arthritis Rheum* 2000; 43: 1858-65.
- AL-MATAR MJ, PETTY RE, TUCKER LB et al.: The early pattern of joint involvement predicts disease progression in children with oligoarticular (pauciarticular) juvenile rheumatoid arthritis. Arthritis Rheum 2002; 46: 2708-15.
- ADIB N, SILMAN A, THOMSON W: Outcome following onset of juvenile idiopathic inflammatory arthritis: Frequency of different outcomes. *Rheumatology* 2005; 44: 995-1001.
- 9. ZAK M, PEDERSEN FK: Juvenile chronic

arthritis into adulthood: a long-term followup study. *Rheumatology* 2000; 39: 198-204.

- PACKHAM JC, HALL MA: Long-term follow-up of 246 adults with juvenile idiopathic arthritis: functional outcome. *Rheumatology* 2002; 41:1428-35.
- OZDAL PC, VIANNA RN, DESCHENES J: Visual outcome of juvenile rheumatoid arthritisassociated uveitis in adults. *Ocul Immunol Inflamm* 2005, 13: 33-8.
- SABRI K, SAURENMANN RK, SILVERMAN ED, LEVIN AV: Course, complications and outcome of juvenile arthritis-related uveitis. *J AAPOS* 2008, 12: 539-45.
- 13. VIOLA S, FELICI E, MAGNI-MANZONI S *et al.*: Development and validation of a clinical index for assessment long-term damage in juvenile idiopathic arthritis. *Arthritis Rheum* 2005; 52: 2092-102.
- 14. SARMA PK, MISRA R, AGGARWAL A: Physical disability, articular, and extra-articular damage in patients with juvenile idiopathic arthritis. *Clin Rheumatol* 2008; 27: 1261-5.
- SOLARI N, VIOLA S, PISTORIO A *et al.*: Assessing current outcomes of Juvenile Idiopathic Arthritis: a cross-sectional study in a tertiary center sample. *Arthritis Rheum* 2008; 59: 1571-9.
- RUSSO RAG, KATSICAS MM: Global damage in systemic juvenile idiopathic arthritis: preliminary early predictors. *J Rheumatol* 2008; 35: 1151-6.
- 17. SARMA PK, MISRA R, AGGARWAL A: Outcome in patients with enthesitis related arthritis (ERA): juvenile arthritis damage index (JADI) and functional status. *Pediatr Rheumatol Online J* 2008; 6: 18.
- PETTY RE, SOUTHWOOD TR, MANNERS P et al.: International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004; 31: 390-2.
- STEINBROCKER O, TRAEGER CH, BATTER-MAN RC: Therapeutic criteria in rheumatoid arthritis. JAMA 1949; 140: 659-62.
- WALLACE CA, RUPERTO N, GIANNINI EH: Preliminary criteria for clinical remission for select categories of juvenile idiopathic artrhritis. J Rheumatol 2004; 31: 2290-4.
- MACHADO CS, RUPERTO N, SILVA CH et al.; for the PAEDIATRIC RHEUMATOLOGY INTERNATIONAL TRIALS ORGANISATION (PRINTO): The Brazilian version of the Childhood Health Assessment Questionnaire – CHAQ and the Child Health Questionnaire – CHQ. Clin Exp Rheumatol 2001; 19 (Suppl. 23): S25-30.
- 22. RUPERTO N, RAVELLI A, LEVINSON JE *et al.*: Long-term health outcomes and quality of

life in American and Italian inception cohorts of patients with juvenile rheumatoid arthritis: II Early predictors of outcome. *J Rheumatol* 1997; 24: 952-8.

- 23. FERNANDES TA, CORRENTE JE, MAGAL-HÃES CS: Remission status follow-up in children with juvenile idiopathic arthritis. J Pediatr (Rio J) 2007; 83: 141-8.
- SHARMA S, SHERRY DD: Joint distribution at presentation in children with pauciarticular arthritis. J Pediatr 1990; 134: 642-3.
- 25. MARVILLET I, TERRADA C, QUARTIER P, QUOC EB, BODAGHI B, PRIER AM: Ocular threat in juvenile idiopathic arthritis. *Joint Bone Spine* 2009; 76: 383-8.
- 26. BOLT IB, CANNIZZARO E, SEGER R, SAU-RENMANN RK: Risk factors and long-term outcome of juvenile idiopathic arthritis-associated uveitis in Switzerland. *J Rheumatol* 2008; 35: 703-6.
- 27. ZANNIN ME, BUSCAIN I, VITTADELLO F et al.: Timing of uveitis onset in oligoarticular juvenile idiopathic arthritis (JIA) is the main predictor of severe course uveitis. Acta Ophthalmologica 2009 Dec 21 [Epub ahead of print].
- 28. GARE BA, FASTH A: The natural history of juvenile chronic arthritis: a population based cohort study. I. Onset and disease process. J *Rheumatol* 1995; 22: 295-307.
- 29. GARE BA, FASTH A: The natural history of juvenile chronic arthritis: a population based cohort study. II. Outcome status. *J Rheumatol* 1995; 22: 308-19.
- 30. FLATO B, LIEN G, SMERDEL A *et al.*: Prognostic factors in juvenile rheumatoid arthritis: a case–control study revealing early predictors and outcome after 14.9 years. *J Rheumatol* 2003; 30: 386–93.
- 31. SAURENMANN RK, LEVIN AV, FELDMAN BM et al.: Prevalence, risk factors, and outcome of uveitis in juvenile idiopathic arthritis: a long-term follow-up study. Arthritis Rheum 2007; 56: 647-57.
- 32. SANDBORG C, HOLMES TH, LEE T et al.: Candidate early predictors for progression to joint damage in systemic juvenile idiopathic arthritis. J Rheumatol 2006; 33: 2322-9.
- 33. BLOOM BJ, ALARIO AJ, MILLER LC: Intraarticular corticosteroid therapy for juvenile idiopathic arthritis: report of an experiential cohort and literature review. *Rheumatol Int* 2010 Feb 14 [Epub ahead of print].
- 34. MAGNANI A, PISTORIO A, MAGNI-MANZONI S et al.: Achievement of a state of inactive disease at least once in the first 5 years predicts better outcome of patients with polyarticular juvenile idiopathic arthritis. J Rheumatol 2009; 36: 628-34.

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