Global Damage in Systemic Juvenile Idiopathic Arthritis: Preliminary Early Predictors

RICARDO A.G. RUSSO and MARÍA M. KATSICAS

ABSTRACT. ***Objective.*** To assess damage in systemic juvenile idiopathic arthritis (sJIA) by the use of the Juvenile Arthritis Damage Index (JADI) and to identify early predictors of global, articular, and extraarticular damage.

Methods. Forty-seven consecutive patients with sJIA with a disease duration > 24 months were assessed for damage in a cross-sectional evaluation. The JADI was administered by 2 pediatric rheumatologists. Damage was defined as JADI score ≥ 1. Early clinical variables were retrieved from clinical records, and they included demographic, clinical, and laboratory characteristics. Univariate analysis was used to select candidate predictors to be included in multiple logistic regression.

Results. Twenty (43%) patients exhibited damage: 18 (38%) patients had articular and 9 (19%) extraarticular damage. JADI score ranged between 0 and 24. Cervical spine arthritis and corticosteroid usage occurring in the first 6 months of the disease course were found as predictors of damage. Damage scores correlated with number of joints with limited motion, and with functional disability.

Conclusion. Articular damage is the main component of global damage in patients with sJIA. Early cervical spine involvement and corticosteroid usage may identify patients with sJIA at risk of developing damage. (First Release April 1 2008; J Rheumatol 2008;35:1151–6)

Key Indexing Terms:
JUVENILE SYSTEMIC ARTHRITIS DAMAGE DISABILITY OUTCOME MEASURES

Juvenile idiopathic arthritis (JIA) is a common chronic illness of childhood with a prevalence of about 1 per 1000 children[1]. The systemic subset of JIA (sJIA) accounts for about 15% of children diagnosed with JIA. The main features of sJIA are chronic arthritis and various extraarticular features that include quotidian high fever, evanescent erythematous rash, serositis, hepatosplenomegaly, lymphadenopathy, leukocytosis, thrombocytosis, and anemia[2]. Longterm followup studies have shown that 30% to 65% of patients with sJIA develop a debilitating, destructive arthritis that leads to chronic disability and significant functional impairment. Moreover, these patients usually have significantly worse functional outcomes, more school limitations, impaired linear growth, and radiographic damage than children with other types of JIA[3-5]. Avascular necrosis of bone, muscle atrophy, cataracts, and other extraarticular sequelae that have been related to prolonged corticosteroid usage are long-lasting or even irreversible changes that contribute to global damage in some patients with sJIA[6-9].

Measuring damage in sJIA may become an objective tool for following patients and allowing comparisons between series. Unfortunately, there are some difficulties when comparing followup studies in patients with sJIA. Previous investigations have mainly focused on radiographic joint damage as the main outcome measure, but unfortunately different methods for its assessment were used[10-13]. Study samples have been heterogeneous, and definition of damage has varied among investigations. Assessment of damage through a standard method may allow comparison. The Juvenile Arthritis Damage Index (JADI), a new tool designed to measure damage in patients with juvenile arthritis, has been recently proposed by Viola, *et al*[14]. It is a composite score that includes items of persistent articular and extraarticular changes. Viola, *et al* defined damage as "persistent changes in anatomy, physiologic status, pathologic processes, or function, that is the result of prior active disease, complications of therapy, or co-morbid conditions, that is not due to currently active arthritis, and that is present for at least 6 months despite previous therapies, including exercise and rehabilitation"[14].

Identifying patients with a high likelihood of developing damage is important for their optimal management. Prediction of the development of damage would aid in the choice of rational therapeutic strategies. Several investigators have identified different early clinical and laboratory predictors of disease outcome, course, and radiographic damage[10-13,15-18]. The goals of our study are to assess dam-

From Servicio de Inmunología y Reumatología, Hospital de Pediatría "Prof. Dr. Juan P. Garrahan," Buenos Aires, Argentina.

R.A.G. Russo, MD; M.M. Katsicas, MD.

Address reprint requests to Dr. R.A.G. Russo, Servicio de Inmunología y Reumatología, Hospital de Pediatría "Prof. Dr. Juan P. Garrahan," Pichincha 1880 (1245), Buenos Aires, Argentina.

Accepted for publication January 14, 2008.

age by the use of the JADI and to identify early predictors of global, articular, and extraarticular damage in patients with sJIA.

MATERIALS AND METHODS

Patient selection. Our study comprised all patients consecutively seen between July 2005 and January 2007 at the Service of Immunology and Rheumatology of the Hospital de Pediatría "Prof. Dr. Juan P. Garrahan," a tertiary referral center. Criteria for inclusion in the study included definite diagnosis of sJIA according to the criteria of the International League of Associations for Rheumatology[19], evaluation at the Service of Immunology and Rheumatology within 6 months of disease onset, disease duration ≥ 2 years, and complete records available from the time of diagnosis. Information was retrospectively collected from the patients' case histories and the database of our service, and it included sex, age at disease presentation, and the following data recorded in the first 6 months since disease onset: clinical features [presence of fever, rash, hepatomegaly, splenomegaly, generalized lymphadenopathy, serositis, pattern of articular involvement (large, small, upper limb, and lower limb joints, cervical spine), individual joint involvement, number of joints with active arthritis (i.e., number of swollen or effused joints, or joints having at least 2 of the following features: increased heat, limited range of motion, and tenderness or pain on movement)[20]]; treatment data (any usage of systemic corticosteroids); and laboratory data [highest observed white blood cell (WBC) count (cells × 10^9/l), highest observed neutrophil count (cells × 10^9/l), highest observed platelet count (platelets × 10^9/l), highest observed erythrocyte sedimentation rate (ESR; mm/h), lowest observed hemoglobin level (g/dl)]. A "highest (or lowest) observed" value was the largest (or smallest) value observed on a measure over the period of interest (0–6 months) chosen to represent the extreme manifestation of a variable. Patients were followed up at regular intervals of 3–6 months. Data pertaining to history and examination findings were collected using a standardized form that was completed at clinic or inpatient visits during the study period. Laboratory data were obtained from the Service of Immunology and Rheumatology clinical database, including all in-hospital and outpatient results.

Clinical assessment. At the time of the damage assessment visit, the following clinical variables were examined and recorded by the attending pediatric rheumatologist: age, disease duration, disease course (monocyclic, polycyclic, or persistent, according to the classification defined by Lomater, *et al*[7]), previous usage of systemic corticosteroid [cumulative dose (g), total time of therapy], number of swollen joints, number of joints with pain or tenderness on movement, number of joints with limited range of motion, number of joints with limited range of motion unrelated to inflammation (i.e., with no other features of active arthritis), number of joints with active arthritis (or active joints). A radiographic assessment was performed based on the most recent radiographs obtained in the previous year for each patient. For the purposes of our study, cervical spine, wrist, and hip radiographs were evaluated and radiographic damage was defined as presence of bony erosions or fusion. Cartilage loss was not evaluated because older radiographs that were needed for comparative assessment were not available for a substantial proportion of patients.

A parent of each patient was asked to complete the Argentinian version of the Childhood Health Assessment Questionnaire (C-HAQ)[21] (0: best, 3: worst). For purposes of the analysis, the C-HAQ score was divided into 2 categories: 0–0.5: mild disability; > 0.5: moderate to severe disability.

Assessment of damage. The amount of damage, defined as the presence of changes in anatomy, physiologic status, pathologic processes, or function, that is not due to currently active arthritis and that is present for at least 6 months, was determined independently by 2 pediatric rheumatologists using the JADI[14]. According to this score, articular damage assessment relies basically on the presence of limitation of range of motion, contractures, and other joint deformities that are not related to joint inflammation, and/or presence of severe bone involvement (ankylosis or prosthesis). As proposed by its authors and using their definitions, articular and extraarticular damage was assessed and scored for the 2 components of JADI, JADI-A (maximum total score 72) and JADI-E (maximum total score 17), respectively. Damage observed in each joint was scored on a 2-point scale. The JADI-E included 13 items (in 5 different systems), which were scored as either 0 or 1 according to whether damage was absent or present, respectively. All assessments were performed the same day. Damage assessment was repeated after ≥ 6 months of the first observation. Items that were abnormal on both assessments were scored as present in the final scoring. The primary outcome variable, global damage, was defined as the presence of JADI score ≥ 1. Articular damage was defined as the presence of JADI-A score ≥ 1, and extraarticular damage as JADI-E score ≥ 1.

Statistical analysis. For the purposes of our study, the patient population was divided into 2 groups: Group 1, which included patients with evidence of damage as defined by JADI score ≥ 1; Group 2, which included patients with absence of damage as defined by JADI score = 0. Student t test for normally distributed variables, Mann-Whitney U-test for non-normally distributed variables, and Fisher exact test for categorical variables were used for comparisons between Groups 1 and 2.

To identify predictors of damage, univariate single logistic regression analysis was performed in the first phase, with the variables assessed within the first 6 months after disease onset serving as candidate predictors, and presence or absence of damage serving as the dependent variable. All clinical and laboratory independent variables showing p value < 0.05 in the univariate analysis were analyzed as possible predictors in the multivariate analysis using backward stepwise elimination techniques. Data on the strength of the associations were expressed as odds ratios (OR) per unit change of the independent variable and 95% confidence intervals (CI). Correlations between JADI scores and different outcome measures were performed through the Spearman's correlation test. For the purpose of this analysis, correlations > 0.7 were considered high, correlations ranging from 0.4 to 0.7 moderate, and correlations < 0.4 low[22]. Separate analyses for global (JADI), articular (JADI-A), and extraarticular (JADI-E) damage scores were performed. Interrater agreement was assessed through the intraclass correlation coefficient (ICC). All statistical analyses were performed with SPSS software (SPSS Inc., Chicago, IL, USA).

RESULTS

Characteristics of the study sample. A total of 47 patients (29 girls) were included in the study. Age at disease onset was 5 (range 0.7–13) years and duration of symptoms at first evaluation was 2 (range 0.2–6) months. Clinical and laboratory features during the initial 6 months of the disease course are summarized in Table 1.

The characteristics of patients at the time of damage assessment are summarized in Table 2. Previous treatment had included nonsteroidal antiinflammatory drugs in 47 patients, methotrexate in 43, systemic corticosteroids in 40, and tumor necrosis factor blockers in 20. The indication for systemic corticosteroid therapy was refractory inflammatory anemia, serositis, macrophage activation syndrome, or uncontrollable, persistent systemic activity. Twenty (43%) patients showed JADI scores ≥ 1 and were included in Group 1, while 27 patients had a JADI score = 0 and were included in Group 2. Interobserver agreement was considered to be good (ICC 0.86). Articular disease activity was more frequent and severe in patients belonging to Group 1, who had presented a persistent course more frequently than patients in Group 2. Mean JADI scores for the whole sample were: JADI 2.47 (median 0, range 0–24); JADI-A 1.98 (0, 0–20); and JADI-E 0.49 (0, 0–4). The JADI scores as

Table 1. Clinical and laboratory features during the first 6 months of the disease course.

	Group 1 JAD1 > 1 (n = 20)	Group 2 JADI = 0 (n = 27)	p
Age at disease onset, yrs	5.5 (3–7.7)	5 (2.2–8.7)	NS
Sex (female)†	13 (65)	16 (59)	NS
Rash†	13 (65)	22 (81)	NS
Hepatomegaly†	5 (25)	9 (33)	NS
Splenomegaly†	4 (20)	6 (22)	NS
Lymphadenopathy†	11 (55)	15 (55)	NS
Serositis†	4 (20)	3 (11)	NS
Polyarticular arthritis†	17 (85)	20 (74)	NS
No. of active joints*	16.5 (6.2–20)	6 (3–10)	0.02
No. of tender joints*	15 (5–19)	5 (3–9)	0.01
No. of swollen joints*	14 (5–20)	5 (3–10)	0.03
No. of joints with limited range of motion*	6.5 (3–9)	2 (1–3)	0.03
Leukocyte count ($\times 10^9$/l)*	21.8 (16–27.7)	19.2 (8.3–44.0)	NS
Neutrophil count ($\times 10^9$/l)*	17.0 (13.7–25.1)	16.0 (8.9–18.6)	NS
Hemoglobin, g/dl*	8.9 (8–10)	10.2 (9.5–10.7)	0.01
Platelet count ($\times 10^9$/l)*	632 (518–850)	523 (375–727)	NS
ESR, mm/h*	120 (76–125)	104 (70–120)	NS
Use of corticosteroids†	17 (85)	12 (44)	0.001
Articular involvement			
Cervical spine†	17 (85)	13 (48)	0.01
Wrist†	19 (95)	20 (74)	NS
Hip†	8 (40)	9 (33)	NS
Large joints†	20 (100)	25 (93)	NS
Small joints†	16 (80)	15 (55)	NS
Upper limb joints†	19 (95)	22 (81)	NS
Lower limb joints†	20 (100)	25 (93)	NS

Values represent *median (interquartile range), or † number of patients (%). JADI: Juvenile Arthritis Damage Index; ESR: erythrocyte sedimentation rate; NS: not significant.

well as the frequency of positive individual articular and extraarticular components corresponding to patients included in Group 1 are shown in Table 3. Eighteen (38%) patients showed damage in at least 1 articular site and 9 (19%) children exhibited extraarticular damage. Radiographs of wrist, cervical spine, and hip joints were available for 29 patients (19 in Group 1 and 10 in Group 2) who had exhibited abnormal findings in those sites during the previous year. Radiographic damage was present in 17 (59%) examined patients: wrist in 12, cervical spine in 10, and hip in 8 children. Erosions were observed in 15 (52%) and fusion in 12 (41%) patients. Sixteen (94%) patients who showed radiographic damage had a JADI-A score ≥ 1.

Predictors of damage. Global damage: Univariate analysis disclosed a significant relative risk of damage for the following variables occurring in the period 0–6 months: cervical spine arthritis (p = 0.01), number of active joints (p = 0.02), lower hemoglobin levels (p = 0.01), and corticosteroid usage (p = 0.01). Multiple logistic regression analysis identified cervical spine arthritis (p = 0.01, OR 7.01, 95% CI 1.49–32.88) and corticosteroid usage (p = 0.01, OR 7.01, 95% CI 1.49–32.88) as significant predictors of damage.

Articular damage: The following early variables showed significant association with articular damage in univariate analysis: number of active joints (p = 0.004), cervical spine arthritis (p = 0.01), presence of small joint arthritis (p = 0.01), and corticosteroid usage (p = 0.01). Multivariate analysis identified cervical spine arthritis (p = 0.04, OR 6.20, 95% CI 1.09–35.28) and number of active joints (p = 0.02, OR 1.13, 95% CI 1.02–1.25) as significant predictors of damage.

Extraarticular damage: Univariate analysis disclosed a significant relative risk of damage for higher ESR (p = 0.006), and lower hemoglobin levels (p = 0.004), but no modeling in multiple logistic regression analysis could identify significant predictors of damage.

Association between JADI scores and measures of disease activity and permanent change. Spearman's correlation coefficients are shown in Table 4. Correlation between JADI or JADI-A scores and number of joints with limited motion unrelated to activity was considered to be high (≥ 0.70), while correlation between these scores and measures of disease activity was moderate (0.40–0.64). No significant correlation was found between JADI scores and disease duration. Total time of corticosteroid exposure correlated significantly with JADI score. On the other hand, JADI-E score was not highly correlated with any outcome measure of activity or permanent change.

DISCUSSION

Forty-three percent of patients with sJIA showed persistent changes in articular and extraarticular structures and functions that could be defined as damage after a median disease course of 6 years. Articular damage was most common in hip, wrist, and temporomandibular joints (TMJ), while growth failure, muscle atrophy, and avascular necrosis of bone were the most frequent extraarticular damage components. Articular damage was the most important component of global damage in our patients, representing almost 80% of the total JADI score. This is the first reported specific assessment of damage in patients with sJIA through the use of JADI, a validated, objective, and quantitative score. We were also able to identify cervical spine arthritis as a prognostic factor of global and articular damage.

The JADI was first used to assess damage by Viola, *et al* in a group of 158 patients with different categories of JIA (12.6% of patients had sJIA)[14]. Articular damage was present in 47% of patients, while 37% of the examined children evidenced extraarticular damage in their report. These percentages are higher than those we found in our cohort. This difference is likely to be related to the sample composition, since the group reported by Viola, *et al* exhibited a significantly longer disease duration. Even though correlation between disease duration and damage was not high in our

Table 2. Patients' characteristics at the time of damage assessment.

	Group 1 JAD1 > 1 (n = 20)	Group 2 JADI = 0 (n = 27)	p
Age, yrs*	14 (5–17)	10 (8–14)	NS
Disease duration, yrs*	7 (4.2–10)	4.5 (3.2–7.5)	NS
Corticosteroid exposure, yrs*	3 (1.7–6.1)	0.5 (0.2–1.6)	0.001
Corticosteroid dose, g*	6.8 (4.4–13.1)	1.9 (0.1–3.9)	0.001
No. of active joints*	2 (0–6)	0 (0–0)	0.01
No. of tender joints*	0 (0–1)	0 (0–0)	0.03
No. of swollen joints*	2 (0.2–5.5)	0 (0–0)	0.01
No. of joints with limited range of motion*	5 (2.2–12.5)	0 (0–0)	0.001
No. of joints with limited range of motion related to inflammation*	2 (0–3.7)	0 (0–0)	0.001
No. of joints with limited range of motion unrelated to inflammation*	3.5 (1–5)	0 (0–0)	0.001
Inactive disease†	5 (25)	23 (85)	0.001
Articular activity†	15 (75)	4 (15)	0.001
Systemic activity†	2 (10)	3 (11)	NS
Functional capacity (CHAQ)			
CHAQ score 0–0.5†	13 (65)	27 (100)	0.001
CHAQ score > 0.5†	7 (35)	0 (0)	0.001
Radiographic damage†	16/19 (84)	1/10 (10)	0.001
Disease course			
Monocyclic†	4 (20)	9 (33)	NS
Polycyclic†	0 (0)	9 (33)	0.01
Persistent	16 (80)	9 (33)	0.001

Values express * median (interquartile range), or † number of patients (%).

Table 3. Results of Juvenile Arthritis Damage Index (JADI) assessment in 20 patients with sJIA who exhibited damage (Group 1).

JADI Scores	Median	Average	Range
JADI score	4	5.8	1–24
JADI-A score	3	4.65	1–20
JADI-E score	0.5	1.15	0–4
Frequency of individual components of JADI score, n of patients (%)			
Articular			
Hip		10	(50)
Wrist		9	(45)
Temporomandibular		8	(40)
Cervical spine		7	(35)
Knee		4	(20)
Proximal interphalangeal		4	(20)
Shoulder		3	(15)
Metatarsophalangeal		2	(10)
Ankle		1	(5)
Elbow		1	(5)
Extraarticular			
Growth		6	(13)
Muscle atrophy		4	(8)
Avascular necrosis		4	(8)
Leg-length discrepancy		3	(6)
Scoliosis		2	(4)
Cataracts		1	(2)
Striae rubrae		1	(2)
Pubertal delay		1	(2)

Table 4. Correlation between JADI scores and outcome measures.

Measure	JADI Score	JADI-A Score	JADI-E Score
No. of active joints	0.64	0.62	0.40
No. of tender joints	0.39	0.39	0.37
No. of swollen joints	0.64	0.62	0.55
No. of joints with limited motion	0.85	0.83	0.49
No. of joints with limited motion related to inflammation	0.63	0.60	0.56
No. of joints with limited motion unrelated to inflammation	0.74	0.74	0.54
Functional capacity (C-HAQ)	0.76	0.76	0.59
Disease duration	0.36	0.40	0.18
Corticosteroid exposure	0.70	0.65	0.60
Corticosteroid dose	0.70	0.65	0.50

JADI: Juvenile Arthritis Damage Index (A = articular component; E = extraarticular); C-HAQ: Childhood Health Assessment Questionnaire.

analysis, these variables showed significant association in the Viola study[14].

Assessment of articular damage through the JADI relies mainly on the limitation of range of motion in a wide set of joints. As shown by Bekkering, *et al*[23], loss of joint motion

is the strongest indicator of functional disability in children with sJIA. In our population, the JADI-A score was highly correlated not only with number of joints with limited range of motion but with C-HAQ score as well, supporting that observation. However, although it is intended to measure only irreversible changes, there is a possibility that the JADI measured not only irreversible but also reversible abnormalities (activity) in our cohort. In our study, patients who exhibited damage had significantly more active disease than patients without damage. Since limitation of range of motion is one of the components of the definition of an active joint, assessment of damage through the JADI may have included some active joints as damaged. Palmisani, *et al* found a moderate to high correlation between number of swollen joints and number of joints with limited range of motion in patients with JIA[24].

In accord with previous followup studies[4,5,7,8,11,13], hips, wrists, cervical spine, and TMJ were the most frequently affected joints in our cohort. Cabane, *et al* found that hips, wrists, and cervical spine were the most frequently and severely affected joints in a small group of patients with sJIA and adult-onset Still's disease[25]. In a more recent report, patients with sJIA exhibited more frequent hip joint destruction than patients with polyarticular or oligoarticular JIA[26]. Similarly, both cross-sectional and longitudinal studies have disclosed a high frequency of TMJ involvement in patients with sJIA (49% to 67%) as compared to other forms of JIA[4,27,28].

Cervical involvement in the first 6 months of disease course emerged as one of the independent predictors of global and articular damage in our cohort. An association between early cervical spine involvement and subsequent damage has also been reported by other investigators[12,29]. Modesto, *et al* found early cervical spine arthritis was associated (in univariate analysis) with a bad articular outcome, defined as the persistence of inflammatory symptoms and/or established limitation of the range of motion, in patients with sJIA[12]. Interestingly, limitation of range of motion was used as a dependent variable in that study. Similarly, we focused on damage as defined by the JADI (permanent, moderate to severe limitation of range of motion) as the outcome measure to test early predictors.

The use of systemic corticosteroid therapy for the control of early persistent systemic inflammatory activity during the first 6 months of disease course was also identified as a predictor of damage in our cohort. This is in accord with previous reports[10,15]. Schneider, *et al* showed that persistent systemic symptoms and thrombocytosis at 6 months after disease onset were predictive of a chronic, polyarticular arthritis course and early radiographic evidence of joint damage in children with sJIA[10]. Similarly, Spiegel, *et al* found the predictor value of early corticosteroid therapy (as well as the presence of fever and thrombocytosis) for poor functional outcome in a large cohort of children with systemic arthritis[15].

Our study should be interpreted in light of its limitations, such as retrospective retrieval of data and assessment of patients from a single center. The sample size was small and therefore the statistical significance of associations may be different in larger populations. Moreover, radiographic assessment could only be performed in children with symptomatic joints, and quantitative methods for measuring radiographic damage were not used in our study[30,31].

Our study shows that global damage in sJIA is present in a significant proportion of patients and it is mostly dependent on its articular component. Also, cervical spine involvement and corticosteroid usage (motivated by persistent systemic activity) in the first 6 months of the disease course may be valuable for the identification of patients with sJIA at risk of developing damage and poor functional outcome. These prognostic factors, together with other well known clinical measures of higher risk of a bad outcome, should be regarded as helpful markers when deciding upon the best treatment strategy early in the followup of patients with sJIA.

REFERENCES

1. Cassidy JT, Petty RE. Chronic arthritis in children. In: Cassidy JT, Petty RE, Laxer RM, Lindsley CB, editors. Textbook of pediatric rheumatology. 5th ed. Philadelphia: Elsevier Saunders; 2005:206-60.
2. Petty RE, Cassidy JT. Systemic arthritis. In: Cassidy JT, Petty RE, Laxer RM, Lindsley CB, editors. Textbook of pediatric rheumatology. 5th ed. Philadelphia: Elsevier Saunders; 2005:291-303.
3. Bowyer SL, Roettcher PA, Higgins GC, et al. Health status of patients with juvenile rheumatoid arthritis at 1 and 5 years after diagnosis. J Rheumatol 2003;30:394-400.
4. Packham JC, Hall MA. Long-term follow-up of 246 adults with juvenile idiopathic arthritis: functional outcome. Rheumatology Oxford 2002;41:1428-35.
5. Oen K, Malleson PN, Cabral DA, Rosenberg AM, Petty RE, Cheang M. Disease course and outcome in juvenile rheumatoid arthritis in a multicenter cohort. J Rheumatol 2002;29:1989-99.
6. Simon D, Fernando C, Czernichow P, Prieur AM. Linear growth and final height in patients with systemic juvenile idiopathic arthritis treated with longterm glucocorticoids. J Rheumatol 2002;29:1296-300.
7. Lomater C, Gerloni V, Gattinara M, Mazzotti J, Cimaz R, Fantini F. Systemic onset juvenile idiopathic arthritis: a retrospective study of 80 consecutive patients followed for 10 years. J Rheumatol 2000;27:491-6.
8. Svantesson H, Akesson A, Eberhardt K, Elborgh R. Prognosis in juvenile rheumatoid arthritis with systemic onset: a follow-up study. Scand J Rheumatol 1983;12:139–44.
9. Kobayakawa M, Rydholm U, Wingstrand H, et al. Femoral head necrosis in juvenile chronic arthritis. Acta Orthop Scand 1989;60:164-9.
10. Schneider R, Lang BA, Reilly BJ, et al. Prognostic indicators of joint destruction in systemic onset juvenile rheumatoid arthritis. J Pediatr 1992;120:200–5.
11. 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.
12. Modesto C, Woo P, García-Consuegra J, et al. Systemic onset juvenile chronic arthritis: polyarticular pattern and hip involvement

as markers for a bad prognosis. Clin Exp Rheumatol 2001;19:211-7.
13. Magni-Manzoni S, Rossi F, Pistorio A, et al. Prognostic factors for radiographic progression, radiographic damage, and disability in juvenile idiopathic arthritis. Arthritis Rheum 2003;48:3509-17.
14. Viola S, Felici E, Magni-Manzoni S, et al. Development and validation of a clinical index for assessment of long-term damage in juvenile idiopathic arthritis. Arthritis Rheum 2005;52:2092-102.
15. Spiegel LR, Schneider R, Lang BA, et al. Early predictors of poor functional outcome in systemic-onset juvenile rheumatoid arthritis. A multicenter cohort study. Arthritis Rheum 2000;43:2402-9.
16. Singh-Grewal D, Schneider R, Bayer N, Feldman BM. Predictors of disease course and remission in systemic juvenile idiopathic arthritis. Arthritis Rheum 2006;54:1595-601.
17. Oen K, Malleson PN, Cabral DA, et al. Early predictors of longterm outcome in patients with juvenile rheumatoid arthritis: subset-specific correlations. J Rheumatol 2003;30:585-93.
18. Selvaag AM, Lien G, Sorskaar D, Vinje O, Forre O, Flato B. Early disease course and predictors of disability in juvenile rheumatoid arthritis and juvenile spondyloarthropathy: a 3 year prospective study. J Rheumatol 2005;32:1122-30.
19. 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.
20. Brewer EJ, Bass J, Baum J, et al. Current proposed revision of JRA criteria. Arthritis Rheum 1977;Suppl 20:195-9.
21. Moroldo MB, DeCunto C, Hubscher O, et al. Cross-cultural adaptation and validation of an Argentine-Spanish version of the Stanford Childhood Health Assessment Questionnaire (C-HAQ). Arthritis Care Res 1998;11:382-90.
22. Huber AM, Feldman BM, Rennebohm RM, et al. Validation and clinical significance of the Childhood Myositis Assessment Scale for assessment of muscle function in the juvenile idiopathic inflammatory myopathies. Arthritis Rheum 2004;50:1595-603.
23. Bekkering WP, ten Cate R, van Suijlekom-Smit LWA, Mul D, van der Velde EA, van den Ende CHM. The relationship between impairments in joint function and disabilities in independent function in children with systemic juvenile idiopathic arthritis. J Rheumatol 2000;28:1099-105.
24. Palmisani E, Solari N, Magni-Manzoni S, et al. Correlation between juvenile idiopathic arthritis activity and damage measures in early, advanced, and longstanding disease. Arthritis Rheum 2006;55:843-9.
25. Cabane J, Michon A, Ziza J-M, et al. Comparison of long term evolution of adult onset and juvenile onset Still's disease, both followed up for more than 10 years. Ann Rheum Dis 1990;49:283-5.
26. Argyropoulou MI, Fanis SL, Xenakis T, Efremidis SC, Siamopoulou A. The role of MRI in the evaluation of hip joint disease in clinical subtypes of juvenile idiopathic arthritis. Br J Radiol 2002;75:229–33.
27. Pedersen TK, Jensen JJ, Melsen B, Herlin T. Resorption of the temporomandibular condylar bone according to subtypes of juvenile chronic arthritis. J Rheumatol 2001;28:2109-15.
28. Twilt M, Mobers SMLM, Arends LR, ten Cate R, van Suijlekom-Smit LWA. Temporomandibular involvement in juvenile idiopathic arthritis. J Rheumatol 2004;31:1418-22.
29. 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.
30. Poznansky AK, Hernandez RJ, Guire KE, Bereza UL, Garn SM. Carpal length in children — a useful measurement in the diagnosis of rheumatoid arthritis and some congenital malformation syndromes. Radiology 1978;129:661-8.
31. Ravelli A, Ioseliani M, Norambuena X, et al. Adapted versions of the Sharp/van der Heijde Score are reliable and valid for assessment of radiographic progression in juvenile idiopathic arthritis. Arthritis Rheum 2007;56:3087-95.