Analysis of disease activity, functional disability and articular damage in patients with juvenile idiopathic arthritis: a prospective outcome study

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Abstract

Objectives

We longitudinally studied outcomes of patients with juvenile idiopathic arthritis (JIA) using the Childhood Health Assessment Questionnaire (CHAQ) for physical disability and the Juvenile Arthritis Damage Index for articular (JADI-A) and extra-articular damage (JADI-E), and we correlated them with various disease activity variables.

Methods

Eighty-seven patients with JIA were included in the prospective follow-up study with median age 14 years (4.6–18.0), disease duration 5.2 years (2.0–18.9) and follow-up of 4.0 years (2.0–5.2). Besides JADI-A and JADI-E, and the assessment of active joints count, joints with limited mobility, ESR, CHAQ and radiographic damage of joints was also done. A correlation analysis of CHAQ and JADI with various disease activity variables was performed.

Results

The patient's distribution of JIA subtypes were polyarticular (32), systemic onset (13), oligoarticular (31), and enthesitis related arthritis (11). After a follow-up period, 46% patients had active disease compared to 83% patients at baseline ($p<0.01$). The CHAQ disability index improved over baseline, while radiological damage ($p<0.001$) and JADI-A and JADI-E scores worsened ($p<0.001$). CHAQ and JADI significantly correlated with the majority of disease activity variables. CHAQ DI was significantly higher in the patients with coxitis ($p<0.01$) and wrist arthritis ($p<0.001$). The most pronounced deterioration in articular damage (JADI-A) was observed in patients with sJIA (3.69 at baseline vs. 5.69 at study endpoint).

Conclusion

The improvement of functional disability (CHAQ DI) was observed over the course of the disease, whereas radiological joint damage, JADI-A and JADI-E scores worsened. Children with systemic JIA, wrist arthritis, coxitis and prolonged active disease are at higher risk of progression of severe disability.

Key words

juvenile idiopathic arthritis, outcomes, functional disability, articular damage.

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Received on May 19, 2010; accepted in revised form on October 6, 2010.

Competing interests: none declared.

Introduction

Juvenile idiopathic arthritis (JIA) is an autoimmune disorder and the most common paediatric rheumatic disease. Different JIA disease subtypes represent a heterogeneous group of arthropathies characterised by chronic inflammatory arthritis. JIA affects approximately 0.1% of children, and nearly half of the patients continue to have active disease in adult life (1). Early therapy with disease modifying antirheumatic drugs (DMARDs), especially methotrexate, intraarticular glucocorticoids (GC) and biologics have increased the remission rates and improved outcomes in patients with JIA. Several studies have demonstrated a decrease in the numbers of JIA patients with severe disabilities, but the proportion of patients with active disease during adulthood remains similar (2-4). In the majority of JIA patients, disease remission is achieved within the first 5 years of disease duration, after which the probability of remission is significantly reduced (4, 5).

Physical functional disability and articular damage are common in JIA. Studies on functional outcomes of JIA patients showed that a substantial number of JIA patients remain significantly incapacitated. Permanent changes may also occur in extra-articular organs. The most commonly used outcome measure tools, the Childhood Health Assessment Questionnaire (CHAQ) and radiography, have limitations (6). The Juvenile Arthritis Damage Index (JADI), a recently described tool for the assessment of overall articular (JADI-A) and extra-articular damage (JADI-E), has been demonstrated to correlate with parameters of disease activity, different levels of functional disability and radiographic damage of joints (7). Clinical subtype, disease activity and duration, and received therapy may influence the prognosis and outcome in patients with JIA. Since JIA is associated with substantial morbidity and potentially long-term consequences, establishment of early prognostic factors would lead to better management of JIA patients (8).

We undertook a prospective study to evaluate the outcome in patients with JIA who attended a tertiary care hospital. JADI was measured to assess damage, CHAQ was used to assess the functional status and the correlation of JADI and CHAQ with various disease activity measures was performed.

Materials and methods

We undertook a prospective study to evaluate the disease outcomes of patients with JIA. One hundred and forty-five patients aged less than 18 years attended the Institute of Rheumatology, the main tertiary care referral hospital in the country, between 2003 and 2009, and were diagnosed with JIA according to the International League of Associations for Rheumatology (ILAR) criteria (9). Ninety-five patients met the following inclusion criteria: more than 5 years of age and duration of the disease more than 1 year. An exception was a patient aged 4.6 years. We present 87 JIA patients who had complete data at baseline and at the last visit, and were all examined and followed by one paediatric rheumatologist (GS) for 4.0 (2.8–4.4) years. The period between two clinical visits was at least 2 years. Fifty-eight out of the 145 patients with JIA did not participate in the study. Four patients were lost during the observational period, four patients/parents chose not to participate, and the rest of the patients did not meet inclusion criteria since they were either younger than 5 years of age or had a follow up period shorter than 2 years or disease duration less than 1 year. Onset of arthritis or systemic symptoms was taken as the date of onset of disease. A verbal consent was taken from the parents/patients. The study was approved by the ethics committee of the School of Medicine, University of Belgrade, Serbia.

The physical examination, laboratory investigation and assessment of the functional ability and articular damage were done at baseline and at the last clinical visit (study endpoint). At the time of inclusion in the study and at the last visit, the proportion of patients on glucocorticoids (GC), mehotrexate (MTX), and other disease modifying anti-rheumatic drugs or on an anti-TNF agent, etanercept, were recorded.

The impact of arthritis on physical ability was estimated using the Serbian version of the Childhood Health Assessment

Questionnaire (CHAQ) (10). This questionnaire which contains 69 questions regarding usual daily living activities (DLA) was completed by a parent or a child if older than 12 years of age, in the week prior to the clinical visit. The disability index of the CHAQ (CHAQ DI) ranges from 0 (best) to 3 (worst). CHAQ DI represents the average sum of the entire eight areas covered by CHAQ, and was divided into four categories: 0 = no disability, 0.1–0.5 = mild disability and 0.6–1.5 = moderate disability, and >1.5 = severe disability.

Disease activity was assessed according to the criteria reported by Giannini *et al*. (11) which include: a) physician's global assessment (PGA) of disease activity on a 100-mm visual analogue scale (VAS); b) parent's/patient's assessment of overall wellbeing; c) functional ability; d) number of joints with active arthritis; e) number of joints with limited range of motion (LOM); and f) erythrocyte sedimentation rate (ESR). Active joint was defined if joint swelling or any two of the following signs such as limited range of motion (LOM), joint pain/tenderness or joint warmth were present.

Steinbrocker classification (I-IV) of the functional capacity of JIA patients was done (12). Radiological assessment of the affected joints included the x-ray examination of the wrist, knee, hip and feet, and radiographic damage was classified (12) by an experienced radiologist (DJ) who was unaware of patient's diagnosis. Class I is defined as normal, without radiological damage, class II as early changes (periarticular soft tissue swelling, periarticular osteoporosis and joint space narrowing which corresponded with Steinbrocker class 0–II) and class III-IV as late changes (erosion, joint destruction and bone ankylosis).

The assessment of articular and extra-articular damage was assessed by the Juvenile Arthritis Damage Index (JADI) (7). We were given permission by one of the authors (A. Ravelli) to use JADI before it was published, so we were able to use the questionnaire from 2003. The first part of the questionnaire, which refers to articular damage (JADI-A) is defined by the presence of irreversible contractures and other deformities of the joints that are expected to be permanent, without surgical intervention. The articular damage was assessed on both sides of the joints, except for temporomandibular joints which were counted as one. JADI-A scores assess the damage of temporomandibular joints, cervical spine, shoulders, elbows, wrists, methacarpophalangeal and interphalangeal proximal joints, hip, knee, ankle and methatarsophalangeal joints. The maximum possible JADI-A score is 72.

The second part of the questionnaire refers to extra-articular damage (JADI-E), which occurred after disease onset as a result of treatment or intercurrent illness, provided that the damage is irreversible and present for a minimum of 6 months. JADI-E evaluates 5 body systems: eye, skin, musculo-skeletal and endocrine systems, and kidneys (secondary amyloidosis). Extra-articular damage was scored as 0 (absent) or 1 (present). In the case of eye damage, surgical intervention was scored as 2 and permanent blindness as 3. The maximum possible JADI-E score is 17.

Based on the disease history, joint examination and erythrocyte sedimentation rate (ESR) (Westergreen method, normal value <15mm/h for females, <20mm/h for males) disease remission was assessed according to the criteria reported by Wallace *et al*. (13). Inactive disease was defined on the following criteria: no joints with active arthritis, no fever, rash, serositis, splenomegaly, or generalised lymphadenopathy attributable to JIA; no active uveitis; normal ESR or C-reactive protein (CRP); and physician global assessment of disease activity indicates no active disease. Clinical remission on medication (CRM) was defined when inactive disease was present for a period of at least 6 months, and clinical remission off medication (CR) when inactive disease was present for a period of at least 12 months after discontinuation of medication. Overall duration of both, active and remission periods over the course of JIA were recorded.

Statistical methods

Statistical analysis was done using the statistical package SPSS version 16.0. Descriptive statistics and analytical models were applied. Normality of the distribution of the data was assessed by the Kolmogorov-Smirnov test. A comparison of the parametric data was performed by the Student's *t*-test and analysis of variance, and comparison of the non-parametric data by the Mann Whitney, chi-square, McNemar and Kruskal-Wallis tests. The correlation of the CHAQ and JADI with other disease variables was done by Spearman's rank correlation coefficient. A p-*value* ≤ 0.05 was considered as statistically significant, and ≤ 0.01 as highly statistically significant.

Results

The median age at the time of the study of 87 patients with JIA was 14.3 years (range 4.6–18.0 years), and the median duration of disease was 5.2 years (2.0–18.9 years). Two-thirds of the patients were female. Demographic and clinical characteristics of the 87 study patients are shown in Table I.

The treatment modalities at baseline assessment and at the last visit are shown in Table II. Forty-four (50.6%) of the patients started treatment with etanercept in 2006. The number of patients on traditional DMARDs significantly decreased from baseline to study endpoint (65, 74.7% *vs*. 37, 42.5%, McNemar test $p<0.001$), as well as the number of patients treated with MTX, GC and sulphasalasine, but the difference was statistically non-significant. Forty-two (48.3%) patients were treated with oral GC at some time during the course of their disease, for a median of 2.2 years (range 0.1–12).

Disease activity

At study entry, JIA patients were divided into the group with active disease (72, 82.8%) and the group with inactive disease (15, 17.2%) which comprised of 10 (11.5%) patients in clinical remission off medication and 5 (5.7%) patients in clinical remission on medication. Three patients who had inactive disease for less than 6 months were included in the group of patients with clinical remission on medication. The highest number of patients with active

disease was seen among patients with systemic JIA (74, 84.6%), followed by 52 (60.0%) patients with polyarticular JIA RF+ and 43 (50.0%) patients with oligoarticular extended JIA. At the end of a follow-up we observed a significant decrease in the number of patients with active disease (40, 46.0%), with a significant increase in the frequency of patients in remission on medication (23, 26.4%) and remission off medication (24, 27.6%), all $p<0.001$. A significant improvement of disease activity measures was observed as shown in Table III. The number of patients with full range of motion in all joints significantly increased from 18 (20.7%) to 30 (34.5%), ($p<0.001$), and more than half of the patients (49, 56.3%) had no active joints at the final visit. Involvement of the hip was found in 35 (40.2%) patients at baseline, but during the follow-up period 2 additional patients developed coxitis (37, 42.5%). Coxitis was present in 12 (92.3%) patients with sJIA, 14 (62.6%) patients with pJIA RF-, 2 (20%) patients with pJIA RF+, 4 (3.3%) patients with eoJIA, 3 (27.3%) patients with ERA and in 2 (10.5%) patients with oJIA.

The significant drop in ESR values ($p<0.001$) over baseline was noticed. At baseline, 41 (47.1%) patients had normal ESR and 15 (17.2%) patients had ESR ≥60mm/h. At the end of a follow-up the number of patients with normal ESR increased to 55 (63.2%, $p<0.001$); only 6 patients had ESR in the range of 60–100mm/h, and none had ESR >100mm/h.

Functional disability

An overall decrease in the CHAQ disability index over baseline was observed (0.541 *vs*. 0.389, $p<0.05$). Functional status improved in all JIA subtypes, but the difference in the CHAQ DI from baseline to study endpoint reached statistical significance only in patients with ERA (0.51 *vs*. 0.15, $p<0.05$). Changes in the level of functional ability from baseline to endpoint are shown in Fig. 1.

Patients with sJIA had moderate disability during the disease course (1.18 at baseline *vs*. 0.86 at endpoint, ns), while patients with oJIA had mild disability (0.24 at baseline *vs*. 0.18 at endpoint, ns). Wrist and hip are joints that were chosen for the assessment as being the most vulnerable and prone to rapid damage progression (5). When comparing patients without wrist arthritis (35, 40.2%) to those with wrist involvement (52, 59.8%), a significantly lower CHAQ DI was found in the former group (0.164 *vs*. 0.555, $p<0.01$). Similarly, CHAQ DI was significantly higher in patients with coxitis (37, 42.5%) compared to those without coxitis (50, 57.5%), 0.709 *vs*. 0.167, $p<0.001$.

CHAQ disability index in patients with active disease was in the range of moderate disability (0.731) and significantly higher than in patients in remission on medication (0.114) or remission off medication (0.114) ($p<0.001$) as shown in Fig. 2. The majority of patients with remission off medication (19, 79.2%) had no disability (CHAQ = 0) and

Table I. Baseline demographic and clinical features of the 87 study patients with JIA.

Characteristics	Value* (n=87)
Female/male ratio	60/27 (69/31)
Age , median (IQR#), yrs	14.3 (10.8–17.4)
Follow up time, median (IQR), yrs	4.0 (2.8–4.4)
Age at disease onset, median (IQR), yrs	7.0 (3.3–12.0)
Disease duration, median (IQR), yrs	5.2 (3.5–8.5)
Cumulative duration of active phase of disease, median (IQR), yrs	4.9 (3–7.3)
Duration of remission, median (IQR), yrs	3.4 (1.2–7.5)
Time from symptom onset to diagnosis, median (IQR), yrs	0.3 (0.2–0.7)
JIA subtypes	
Systemic (sJIA)	13 (14.9)
Polyarticular, RF negative (pJIA RF-)	22 (25.3)
Polyarticular, RF positive (pJIA RF+)	10 (11.5)
Oligoarticular, persistent (oJIA)	19 (21.8)
Oligoarticular, extended (eoJIA)	12 (13.8)
Enthesitis related arthritis (ERA)	11 (12.6)
ANA positive	34 (39.1)
HLA B27 positive	11 (12.6)
Iridocyclitis	16 (18.4)

*Value refers to the number (%) of patients unless otherwise stated; #IQR-Interquartile range.

Table II. Treatment modalities in 87 patients with JIA.

Treatment	Baseline	Endpoint
Etanercept	0 (0.0)	44 (50.6)
Methotrexate	33 (37.9)	28 (32.2)
Glucocorticoids	15 (17.2)	12 (13.8)
Sulphasalasine	15 (17.2)	9 (10.3)
Hydroxichoquine	4 (4.6)	4 (4.6)
Azatioprine	3 (3.4)	3 (3.4)
Salt gold	1 (1.1)	0 (0.0)

*Values are number (%) of patients.

Table III. Changes from baseline to endpoint in disease activity parameters in 87 patients with JIA.

Disease activity parameters	Baseline	Endpoint	*p*-value
Physician's global assessment, mm*	28.84 ± 24.37	12.62 ± 20.20	<0.001
Parent's/patient's pain assessment, mm*	26.08 ± 26,66	14.69 ± 21.76	<0.001
Parent's/patient's well-being assessment, mm*	25.39 ± 25.38	15.72 ± 23.67	<0.010
Number of joints with LOM (range 0-69)	9.45 ± 12.44	6.34 ± 10.10	<0.001
Number of active joints (range 0-69)	5.55 ± 6.70	2.29 ± 4.78	<0.001
ESR (mm/h)	31.55 ± 29.52	21.21 ± 19.09	<0.001

Values are mean ± SD.
*measured on a 100mm visual analogue scale (0, best; 100, worst). LOM: limited range of motion.

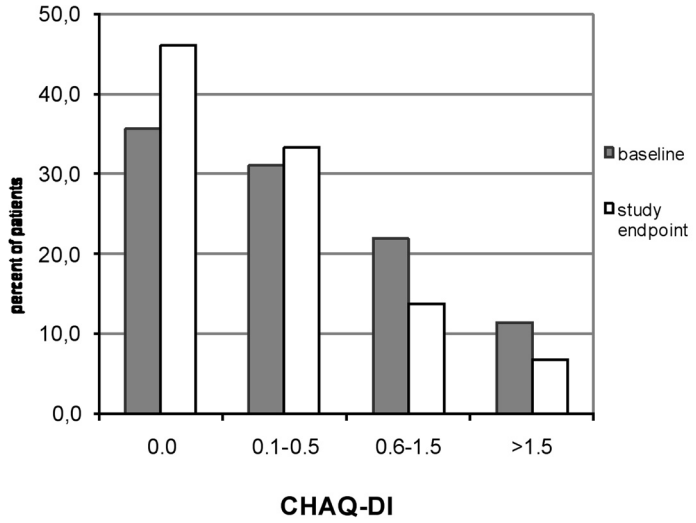

Fig. 1. Change of the disability index of the CHAQ in 87 study patients from baseline to study endpoint

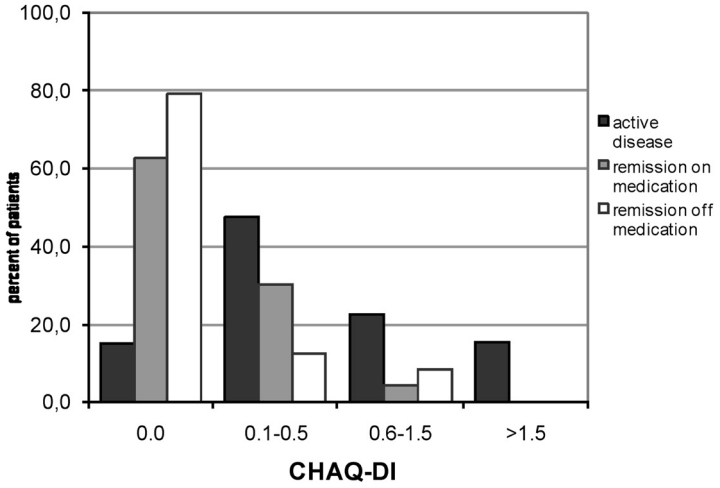

Fig. 2. Disability index of the CHAQ and its relation to disease outcomes in 87 study patients at the last visit

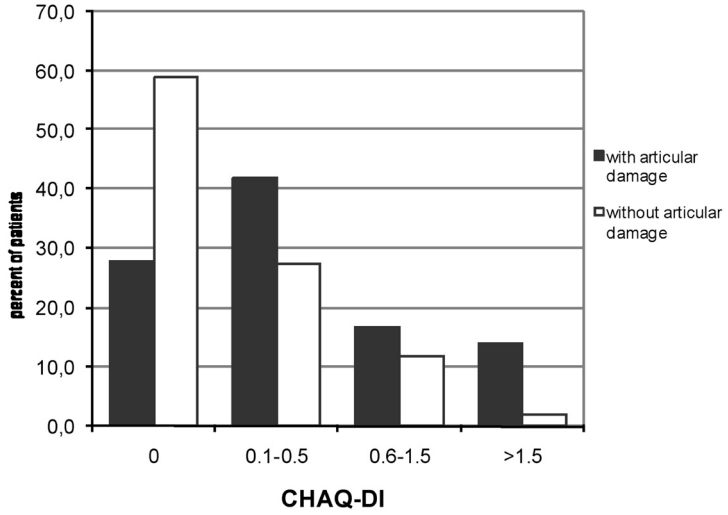

Fig. 3. CHAQ disability index in JIA patients with and without articular damage after a median follow-up of 4 years (n=87)

15 (37.5%) patients in active disease group had moderate-to-severe functional disability (CHAQ ≥0.6). CHAQ DI correlated with the disease outcome (0.569, $p<0.01$).

By the Steinbrocker classification of the functional capacity, two-thirds of patients were in class I (59, 67.8%) at baseline, and this number significantly increased to 76 (87.4%), ($p<0.001$) over time. A significant decrease from 23 (26.4%) to 6 (6.9%) ($p<0.01$) patients in class II was observed. The number of patients in class III remained the same, and none of the patients was in class IV.

Radiological damage

We observed a worsening of radiological damage from baseline to the end of a follow-up: in class I 36 (41.4%) *vs*. 30 (34.5%) patients; in class II 30 (34.5%) *vs*. 26 (29.9%) patients; in class III/IV 21 (24.1%) *vs*. 31 (35.6%) patients ($p<0.001$). Progression of radiological damage was found in all JIA subtypes. Advanced damage, stage III/IV was present in 7 (53.9%) patients with sJIA, in 8 (40.9%) patients with RF- polyarthritis and in 6 (60%) patients with RF+ polyarthritis at the endpoint.

JADI-A and JADI-E

The increase in the number of patients with irreversible articular damage, between 32 (36.8%) patients with ≥1 irreversible joint damage at baseline and 36 (41.4%) patients at the endpoint, was not significant. However, an increase in JADI-A scores at the last clinic visit over baseline was observed (3.00±6.51 *vs*. 3.62±7.33, $p<0.001$). Forty-four (86.3%) patients without articular damage had either normal or mild disability in performing daily living activities (DLA). One-third of patients with JADI index ≥1 had moderate-to-severe functional deficit. CHAQ disability index among JIA patients with or without articular damage is shown in Fig. 3. The highest JADI-A score was found in patients with RF+ polyarthirits at baseline (JADI-A=5.70), and at the last clinic visit (JADI-A=6.50), followed by patients with RF- polyarthritis (JADI-A=5.95 *vs*. 6.60). The most pronounced deterioration in articular damage over the follow-up period was observed in

Table IV. Distribution of damaged joints in JIA patients at the study endpoint.

JADI-A items	Value* (n=36)
Temporomandibular joint	2 (5.6)
Cervical spine	10 (27.8)
Shoulder	9 (25.0)
Elbow	10 (27.8)
Wrist	16 (44.4)
Metacarpophalangeal joints	4 (11.1)
Proximal interphalangeal joints	15 (41.7)
Hip	20 (55.6)
Knee	11 (30.6)
Ankle	12 (33.3)
Metatarsophalangeal joints	7 (19.4)

*Values are number (%) of patients.

Table V. Extra-articular damage in JIA patients at the study endpoint.

Extra-articular damage	Value* (n=34)
Eye damage [a]	7 (20.6)
Growth retardation	7 (20.6)
Pubertal delay	7 (20.6)
Subcutaneous atrophy due to IA. GC	7 (20.6)
Leg-length discrepancy	6 (17.6)
Avascular necrosis	6 (17.6)
Striae rubrae	6 (17.6)
Abnormal vertebral curve	4 (11.8)
Insulin-depended diabetes	2 (5.9)
Osteoporosis	1 (2.9)
Amyloidosis	1 (2.9)
Muscle atrophy	1 (2.9)

*Values are number (%) of patients.
[a] cataract - 2 pts, eye surgery - 2 pts, permanent unilateral blidness - 3 pts.
IA: Intraarticular; GC: glucocorticoid.

patients with sJIA (JADI-A=3.69 *vs*. 5.69). The frequency of JADI-A items at the last clinic visit are presented in Table IV. The number of patients with extra-articular manifestations increased from 23 (26.4%) to 34 (39.1%) ($p<0.01$) and JADI-E scores increased from 0.59±1.29 to 0.84±1.44 ($p<0.001$). The highest proportion of patients with extra-articular damage was found in patients with sJIA (61.5%) followed by patients with eoJIA (58.3%). The frequencies of JADI-E items at the study endpoint are shown in Table V.

Correlation of CHAQ DI and JADI with other disease outcome measures

The CHAQ disability index significantly correlated with the majority of clinical and laboratory parameters of disease activity at the end of a follow-up. The CHAQ DI positively and highly significantly correlated with PGA (0.581), parent's/patient's assessment of the pain (0.559), and well-being (0.485), ESR (0.393), number of active joints (0.565), number of joints with LOM (0.543), cumulative duration of active phases of the disease (0.446), glucocorticoid treatment duration (0.621), functional class (0.488), JADI-A (0.408), JADI-E (0.445). It inversely correlated with remission duration (-0.348), (all $p<0.01$).

The JADI-A positively, highly significantly correlated with the number of joints with limited range of motion (0.675), cumulative duration of active phases the disease (0.351), functional class (0.320), anatomic stage (0.482), JADI-E (0.387), (all $p<0.01$).

By correlating the difference of the CHAQ DI with the difference in the disease activity core set variables endpoint-baseline, we found significant correlation with ESR (0.384), joints with active arthirits (0.435), PGA (0.516), parent/patient's pain assessment (0.504), parent/patient's well-being (0.446), functional class (0.462) (all $p<0.01$).

The difference of articular damage (JADI-A) endpoint-baseline significantly correlated with cumulative duration of active disease (0.274, $p<0.05$) and GC treatment duration (0.422, $p<0.01$).

Discussion

Juvenile idiopathic arthritis is an inflammatory disease that predominantly affects the joints and skeleton in the maturation phase, which is commonly associated with functional disability. JIA begins at an early age and disturbs all aspects of the life of the child and the entire family. (8). A proportion of parents believe that their child will "outgrow" the disease by puberty, but a significant number of patients enter adulthood with active JIA (3, 5, 14). The assessment of functional disability is of fundamental importance in children with JIA.

The aim of this prospective study was to assess outcomes in patients with JIA in a longitudinal manner by examining the disease activity, functional disability and disease damage using CHAQ and JADI, and to see if obtained scores correlate with other disease variables.

Our study showed a decrease in the number of patients with active disease from 83% to 46% after median follow-up of 4 years. This was accompanied with a decrease in the clinical as well laboratory indicators of inflammation. Outcomes improvement may in part be due to etanercept treatment received by more than half of the patients for an average of 20 months. The beneficial and sustained effect of this anti-TNF agent was confirmed in the long-term follow-up study (15). Early recognition and diagnosis of JIA with early initiation of the intensive treatment with DMARDs and biologics, preferable in the 6 months from the illness onset, lead to favourable disease outcome. In our study, the advancement in the patient's body height and weight was observed, which are signs of good disease control (data not shown).

JIA clinical subtype has a strong influence on disease outcome. According to reports, 37% of JIA patients mainly with polyarticular and extended oligoarticular onset continue to have active disease during the average follow-up of more than 20 years (3). Similar to these and the findings of Fantini *et al*. (4), approximately 20% of patients in our study have never achieved remission during the disease course (35% of patients with sJIA and 20% patients with RF+ polyarthritis group) and they will most likely continue to have active disease during adulthood. Physical ability, expressed by the disability index of the CHAQ, significantly improved in our study group. At the last visit, 20.7% of our patients had moderate to severe disability, which is markedly lower than 33.3% of patients at the study entry. These results correspond with the study of Östle *et al*. (16) who reported favourable enhancement of physical as well psychosocial functioning. Nevertheless 38% of patients had variable levels of disability, and 22% had psychiatric distress. In our study, patients with sJIA had more severe disability compared to patients with oJIA who exhibited mild disability, which is

in agreement with the findings of other authors (17). Although oJIA is considered as a benign form of the disease, the evidence shows that the long-term prognosis of this JIA subtype could be underestimated (18).

Hip and wrist joints are most vulnerable and prone to rapid damage and have an important role in daily living activities (DLA) (5, 8, 18). We found that coxitis or wrist arthritis was associated with a more severe disability, *i.e.* CHAQ DI was significantly higher than in patients without hip and wrist involvement. Bandeira *et al.* (19) developed new scoring system that includes cumulative numbers, but also the type of affected joints, according to their importance in performing DLA. In this scoring system which is practical and easy to use, weighting score for hip is the highest. This weighting method deserves further validation in clinical trials.

The CHAQ disability index moderately correlated with all disease activity core set variables, as well as with the parent's/patient's assessment of pain intensity and functional class. The significant association was confirmed when different endpoint-baseline changes were correlated, except for joints with LOM. Joint stiffness, irreversible disease damage, general physical and mental status and especially pain intensity, greatly influence a patient's rating of physical ability. There is also tendency of some parents/patients to underestimate the functional ability. These are the possible reasons for occasional discrepancy between clinical status and PGA with values of the CHAQ disability index. Similar to other studies (20), we also noticed a high degree of inconsistency between the CHAQ scores obtained by either parents or children and disease activity, especially in patients with severe disease.

To override this incongruence, Meiorin *et al.* (21) proposed the Juvenile Arthritis Functional Scale (JAFS), a simple tool that precisely and reliably detects the impairment of joints in specific body areas, and the Serbian version is in the process of being validated.

Active disease with persistent synovial inflammation inevitably leads to joint destruction. Radiological assessment of joint damage has fundamental importance in the evaluation of severity and long-term prognosis of JIA. Contrary to previous opinions, numerous recent studies have shown development of destructive articular changes in children with JIA (22). In this study we evaluated radiological damage in terms of joint erosion, joint space narrowing, ankylosis and subluxation. These anatomical changes reflect previously commenced articular damage and cannot serve as standard prognostic indicators. The most pronounced radiological damage found in our patients with sJIA and RF+ polyarthritis is in agreement with the reported data of the space narrowing and erosions present in nearly all patients with RF+ pJIA in the early course of the disease (20). In our patients radiological damage worsened during the period of observation. At the baseline assessment, 24.0% of patients were in the class III/IV and the number of patients in this anatomical class increased to 35.6% at the end of a follow-up. Radiological damage strongly correlated with JADI-A and functional status, the duration of active disease, the number of active joints and the number of joints with LOM (data not shown). The hip is one of the most vulnerable joints with commonly irreparable radiological damage. All patients except one (92%) in the sJIA group had hip involvement, 54% of them were in III/IV radiological class. Periodical x-ray assessment of affected joints is therefore recommended. According to the reports, coxitis was one of the early risk factors of unfavourable prognosis with the presence of IgM RF, increased long-term ESR, symmetrical arthritis, female gender and younger age at disease onset (8). Gilliam *et al.* (24) indicated the important role of some biomarkers in the pathogenesis of joints damage and its association with disease severity. They found that the serum level of anti-cyclic citrullinated peptide antibodies (anti-CCP), IgM RF, IgA RF and cartilage oligomeric matrix protein (COMP) were significantly higher in patients with erosive disease.

Viola *et al.* (7) has recently proposed a useful tool for measuring articular and extra-articular damage, the Juvenile Arthritis Damage Index (JADI), which has shown good constructive validity when correlated with clinical, laboratory indicators and functional status. Articular damage with JADI ≥1 was present in 36.8% of patients at baseline and in 41.4% of patients at the end of a study. However, the number of patients with articular damage has not increased, but the existing damage has worsened during the observation period. The cumulative period of active disease and GC treatment duration, have important influences on damage progression. Our results are consistent with other studies which have shown similar proportions of JIA patients with high JADI-A and JADI-E scores (25, 26) especially in sJIA and pJIA subtypes. Gurcay *et al.* (27) demonstrated the most pronounced articular damage in patients with RF+ polyarthritis. One of the studies has shown that etanercept had a protective effect on the radiologic articular damage compared to methotrexate, but since this study was uncontrolled; its results need to be confirmed (28).

Our study has several limitations such as the short follow-up period and the small number of patients especially in the different JIA subtypes with a wide range in disease duration. However, the data obtained by using standardised and well-validated outcome measures in this longitudinal study could add to a better understanding of the aggressive nature of JIA and contribute to further research on disease outcome predictors. This is the only longitudinal study of children with JIA in Serbia.

In conclusion, the functional ability has improved in all JIA subtypes over the disease course, as well as all disease activity core set variables. Patients with systemic onset JIA, wrist and hip involvement are at higher risk of progression of severe disability. Despite the improved treatment modalities that successfully control disease activity, radiological, articular and extra-articular damage worsened over time. Long-lasting active disease leads to deterioration of joint damage. Further long-term longitudinal studies on larger sample size of JIA patients are needed to better identify predictors of functional outcomes.

Acknowledgements

We thank Dr A. Ravelli for his helpful comments on the manuscript.

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