Anticitrullinated Protein Antibodies and Radiological Progression in Juvenile Idiopathic Arthritis

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ABSTRACT. ***Objective.*** The aim of the study was to investigate whether determination of anticitrullinated protein antibodies (ACPA) provides predictive information on severity of disease course and joint destruction in children with juvenile idiopathic arthritis (JIA).

Methods. Sera from 74 children with JIA were examined for ACPA using the ELISA test. To assess joint destruction, plain radiographs of both hands were scored twice according to the Steinbrocker scale: at the beginning of observation and after 8.9 to 15.2 months (median 11.5 months) of the followup. Correlations between ACPA serum levels and the disease characteristics (type of JIA onset, disease activity, disease duration, radiological status) were investigated.

Results. Twenty-six out of 74 examined children with JIA (35.0%) were ACPA-positive [> 5 relative units (RU)/ml]. ACPA were present in all types of JIA onset, including 36.6% of children with early stage JIA (disease duration < 6 months). All of the IgM-rheumatoid factor (RF)-positive children with polyarticular type of JIA onset were simultaneously positive for ACPA. ACPA levels correlated positively with disease activity at the beginning of the study (rho = 0.7196; $p < 0.0001$) and after followup (rho = 0.2485; $p = 0.0486$). Disease duration did not significantly affect ACPA serum levels. ACPA levels correlated positively with radiological joint destruction in children with JIA, both at the beginning of the study (rho = 0.4599; $p = 0.0004$) and after the followup period (rho = 0.5523; $p < 0.0001$).

Conclusion. ACPA were superior to IgM-RF in diagnosing JIA and provided predictive information on severity of disease course and radiological outcome. (First Release March 1 2012; J Rheumatol 2012;39:1078–87; doi:10.3899/jrheum.110879)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS — ANTICITRULLINATED PROTEIN ANTIBODIES
DISEASE ACTIVITY — RADIOLOGICAL PROGRESSION

Juvenile idiopathic arthritis (JIA) is the most common systemic autoimmune disease in children[1,2]. The term applies to any arthritis of unknown origin that persists for > 6 weeks resulting in chronic inflammatory lesions in the joints and their progressive destruction, especially during the first 2 years of the disease[3,4,5]. Because the diagnosis of JIA depends mainly on clinical manifestations of the disease, which frequently are not typical, with a limited support from serological markers, it is difficult to confirm JIA, particularly at the early stage of the disease[1,2,3,4,5,6].

Because of the heterogeneity of JIA, the IgM-class rheumatoid factor (IgM-RF), the main immunological marker of adult rheumatoid arthritis (RA), is rarely found in children, most often in the RA-like polyarthritis course of the disease[1,4,6].

The diagnosis of JIA should be established promptly to allow proper therapy, in order to control the progression of rheumatoid process and prevent irreversible destructive changes in the joints[7,8,9,10] and worsening of quality of life[2,3]. Preventing and diminishing the joint damage is an important treatment goal in early RA and patients with JIA[11]. Since the introduction of more potent treatment strategies, the evaluation of radiographic joint damage has become more prominent in the assessment of disease progression in JIA[3,7,8,9,10].

The available data indicate that a considerable number of children with JIA still enter adulthood with persistently active disease, and a significant proportion of them may develop severe physical disability. The comparison of earlier studies with those published in the last decade showed a

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decline in severe physical disability; however, the proportion of children who enter adulthood with active disease does not seem to be smaller[9].

Anticitrullinated protein antibodies (ACPA) were reported to be more specific for RA than is IgM-RF, and they could be detected in up to 80% of patients with RA, with 98% specificity also in RF-negative patients. Observations of patients with RA have shown that ACPA can be an independent predictive factor of the radiological damage and progression[12] and could be useful in identifying patients who would develop the active disease course and more severe joint damage[13,14].

Confirmation of those findings in children with JIA could result in early implementation of more aggressive treatment, to prevent radiological damage of joints. However, unlike RA, only a few studies have considered the value of the new immunological markers in JIA, and opinions on ACPA in JIA seem conflicting[9,10,11,12,13,14,15,16]. Determination of ACPA has been used as a valuable diagnostic tool in RA, with still uncertain significance in JIA[15].

In comparison to RA, only a few studies have evaluated the long-term outcome of JIA and attempted to identify the early prognostic factors analyzing the outcome in terms of clinical remission, physical disability, and radiological damage. So far, prognostic efficacy of the ACPA in predicting clinical and radiological damage in patients with JIA[17,18,19,20,21,22,23,24,25,26] has only been evaluated by Gilliam, *et al*[16]. Therefore, the aim of our study was to investigate whether ACPA provide predictive information on severity of disease course and joint destruction in children with JIA.

MATERIALS AND METHODS

Seventy-four children (47 girls, 27 boys) with JIA, who were hospitalized from 2007-2010 in the Department of Pediatric Cardiology and Rheumatology, Medical University of Lodz, Poland, participated in the study. The patients were included based on the 2001 International League Against Rheumatism classification criteria[5]. They were aged 4–18 years (mean 12.5 ± 4) and in early stages of the disease course (disease duration 0.5–1.5 years, mean 10.0 ± 2 months). They had been treated with disease-modifying antirheumatic drugs (DMARD; methotrexate or/and sulfasalazine) and steroids. Thirty-six children had polyarticular type JIA onset (30 with IgM-RF-negative and 6 with IgM-RF-positive polyarthritis), 29 had oligoarticular JIA (28 with persistent oligoarticular JIA and 1 with extended oligoarticular JIA), and 9 had systemic JIA (Table 1). All of the study group children were biologically naive.

Two groups were distinguished according to the presence of ACPA: 26 ACPA-positive and 48 ACPA-negative children with JIA. Both study groups were compared with sex-matched and age-matched controls.

Serum samples were obtained simultaneously for routine laboratory examinations, including red blood cell, white blood cell, and platelet (PLT) counts, as well as erythrocyte sedimentation rate (ESR; cutoff value > 20 mm/h) or C-reactive protein (CRP; cutoff value > 5 mg/l).

Forty-four out of 74 children with JIA (59.5%) had ESR above 20 mm/h at the beginning of observation and 38/74 (51.4%) after followup. Initially, 54 out of 74 children with JIA (73.%) had CRP above the cutoff value and 43/74 (58.1%) after followup.

The activity of the rheumatoid process was assessed according to the modified Wilkoszewski's criteria as described by Smolewska, *et al*[27]. Three stages of JIA activity were distinguished, based on clinical and laboratory criteria: low activity (limitation of motion, without pain or swelling, no extraarticular symptoms, ESR < 20 mm/h, CRP < 10 mg/l); moderate activity (moderate intensity of arthritis and/or slight temperature, ESR: 20–60 mm/h, CRP: 10–30 mg/l); and high activity (morning stiffness, pain and/or swelling of joints, and/or hepatosplenomegaly, fever, rash, and increased values of inflammation measures: ESR > 60 mm/h, CRP > 30 mg/l). Initially, 20 patients (27.0%) in the examined group had high disease activity; 24 (32.5%) had moderate, and 30 (40.5%) had low (Table 1 and Table 2). After followup, 10 patients (13.5%) had high disease activity, 28 (37.8%) had moderate, and 36 (48.7%) had low.

Table 1. Characteristics of children with JIA (n = 74) at the beginning of observation. Data are n (%) unless otherwise indicated.

Characteristic	
Female	47 (63.5)
Age, yrs, mean ± SD	12.5 ± 4
Type of JIA onset	
Systemic	9 (12.2)
Polyarticular	36 (48.6)
Oligoarticular	29 (39.2)
Disease duration, months, mean ± SD	10 ± 2
ESR-positive (> 20 mm/h)	44 (59.5)
CRP-positive (> 5 mg/dl)	54 (73.0)
IgM-RF positivity (≥ 24 RU/ml)	6 (8.1)
ACPA positivity (≥ 5 RU/ml)	26 (35.1)

JIA: juvenile idiopathic arthritis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor; ACPA: anticitrullinated protein antibodies.

Our study was approved by the local Ethics Committee. In every case, written informed consent was obtained from the parents and patients.

Serum samples from children with JIA were analyzed by commercially available ELISA-detecting ACPA (Euroimmun, Wroclaw, Poland). All serum samples were tested twice. The cutoff value for ACPA positivity recommended by the manufacturer's protocol was > 5 relative units (RU)/ml.

Correlations between ACPA serum concentration levels and the disease characteristics (type of JIA onset, disease activity, disease duration time, radiological status) were investigated. IgM-rheumatoid factor (RF) levels were measured by commercially available ELISA kit (Biomedica, Piaseczno, Poland). According to manufacturer recommendations, sera containing IgM-RF levels > 24 RU/ml were considered IgM-RF-positive.

Conventional plain-film radiographs of both hands and wrists of all study children performed at the beginning of the study and after 8.9 to 15.2 months (median: 11.5 months) of followup were analyzed. The radiographs were assessed in chronological order by a pediatric skeletal radiologist for

Table 2. Disease activity of children with JIA (n = 74). Data are n (%).

Disease Activity*	Beginning of Observation	After Followup
High	20 (27.0)	10 (13.5)
Moderate	24 (32.5)	28 (37.8)
Low	30 (40.5)	36 (48.7)

*High activity [morning stiffness, pain, and/or swelling of joints and/or hepatosplenomegaly, fever, rash, and increased values of inflammation measures: erythrocyte sedimentation rate (ESR) > 60 mm/h, C-reactive protein (CRP) > 30 mg/l]; moderate activity (moderate intensity of arthritis, and/or slight temperature, ESR 20–60 mm/h, CRP 10–30 mg/l); low activity (limitation of motion, without pain or swelling, no extraarticular symptoms, ESR < 20 mm/h, CRP < 10 mg/l).

the presence of the comprehensive spectrum of JIA radiologic features. The radiologist was blinded to the subtype of JIA and the clinical condition of each child. The radiographs were scored using the Steinbrocker assessment method, with a global damage score to hands and wrists on a 4-point scale from I (minimal damage) to IV (severe damage)[7,28]. The grade was determined by the worst change in any joint and therefore the score was given regarding the most severely affected joint. Joint damage was subsequently categorized as progressive when the Steinbrocker score increased. Children with JIA were defined as having a progressive disease course when at least 1 radiographed joint showed progression as defined.

Statistical analysis. The Shapiro-Wilk test was used to examine variable distributions. Variables were analyzed using the nonparametrical Spearman R and Wilcoxon signed-rank tests, chi-squared test, ANOVA Kruskal-Wallis test, generalized linear models, and polychoric correlations, when appropriate. The statistical analysis was performed using the Statistica 9.0 software and Stata/Special Edition (R) release 11.1 for Windows (StataCorp LP, College Station, Texas, USA). Differences were considered significant at p values < 0.05.

RESULTS

ACPA antibodies in children with JIA at the beginning of the observation and after followup. Twenty-six out of 74 of the examined children with JIA (35.1%) were ACPA-positive. Half of that group had the polyarticular type of JIA onset, 8 out of 26 (30.8%) had the oligoarticular type, and 5 out of 26 (19.2%) had the systemic type (Table 1). In the ACPA-negative group, 23 out of 48 (47.9%) children had the polyarticular type of JIA onset, 21 out of 48 (43.8%) had the oligoarticular type, and 4 out of 48 (8.3%) the systemic type.

The frequency of the ACPA-positive cases was the highest in systemic disease (5/9; 55.5%). In children with the polyarticular type of JIA onset, the number of ACPA-positive patients was lower (13/36; 36.1%). All IgM-RF-positive children had the polyarticular type of JIA onset and were simultaneously positive for ACPA. The frequency of the ACPA-positive sera was the lowest in children with oligoarthritis (8/29; 27.5%; Table 3). However, differences were not statistically significant (p > 0.05). No false-positive results of ACPA presence were observed. False-negative ACPA results were observed in 65% of children with JIA.

Table 3. ACPA positivity according to JIA onset type, disease activity, and disease duration at the beginning of the study (out of 26 ACPA-positive patients in the study group). Data are n (%).

Type of JIA onset	
Polyarticular	13 (50.0)
Oligoarticular	8 (30.8)
Systemic	5 (19.20)
Disease activity	
Low	0
Moderate	10 (38.5)
High	16 (61.5)
Disease duration time	
< 6 months	8 (30.75)
6–12 months	8 (30.75)
> 12 months	10 (38.5)

ACPA: anticitrullinated protein antibodies; JIA: juvenile idiopathic arthritis.

Regarding disease activity, the frequency of ACPA positivity was highest in the group of children with a high activity of rheumatoid process (16/20; 80.0%). In the group with moderate activity it was 10/24 (41.7%). None of the low-activity patients had ACPA present in the serum estimated according to the threshold value recommended by the commercial ACPA kit manufacturer (≥ 5 RU/ml).

At the beginning of the study, serum levels of ACPA were found to be significantly higher in children with high activity of the rheumatoid process (rho = 0.72; SE 0.06; p = 0.0001), similar to the results obtained after followup (rho = 0.25; SE 0.093; p = 0.049; Figures 1A and 1B).

Statistically positive correlations were found between ACPA concentration and CRP levels, both at the beginning of observation (rho = 0.54; p = 0.000001) and after the followup period (rho = 0.37; p < 0.001). Similar correlation was observed between ACPA concentration and PLT counts (rho = 0.22; p = 0.0025). Disease duration did not significantly affect the ACPA serum levels (rho = 0.08; SE 0.1170; p = 0.5326; Figure 2).

Nevertheless, positive ACPA levels were more frequently observed in children with disease duration > 1 year (10/21; 47.6%) compared to duration time below 6 months (8/22; 36.6%). ACPA were rarely found in the sera of children with clinical symptoms, who were observed from 6 to 12 months (8/31; 25.8%; Table 3).

The sera from 6 (8.1%) of 74 children with JIA were IgM-RF-positive (≥ 24 RU/ml). IgM-RF was present exclusively in polyarthritis (6/36; 16.7%). IgM-RF prevalence was shown to slightly increase with the longer disease duration – i.e., from 4.5% (1/22) in the sera of children with the disease lasting for a period shorter than 6 months to 14.3% (3/21) in the sera of JIA children, who manifested the symptoms for a period longer than 1 year. No correlation between IgM-RF serum concentration levels and disease activity was observed.

Radiological status of subjects at the beginning of the study and after followup. At the beginning of the study, 42 out of 74 children (56.8%) with JIA were in the Steinbrocker functional class I, 30/74 (40.5%) were in class II, and 2/74 (2.7%) were in class III.

After the followup time, 29 out of 74 children with JIA were in class I in the Steinbrocker scale, 20/74 were in class II, 21/74 were in class III, and 4/74 were in class IV.

While comparing the radiological status at the beginning of the study and after the followup period, a statistically significant difference was found in children with JIA (Z = 5.30; p = 0.0000001; Table 4).

Initially, 24/36 children with polyarthritis were classified as being in class I in the Steinbrocker functional scale, 11/36 as class II, and 1/36 as class III. Four out of 9 children with the systemic type of JIA were in the Steinbrocker class I, 3/9 were in class II, and 2/9 were in class III. Initially, 27/29 children with oligoarthritis were in class I in the Steinbrocker scale, and 2/29 were in class II (Table 4).

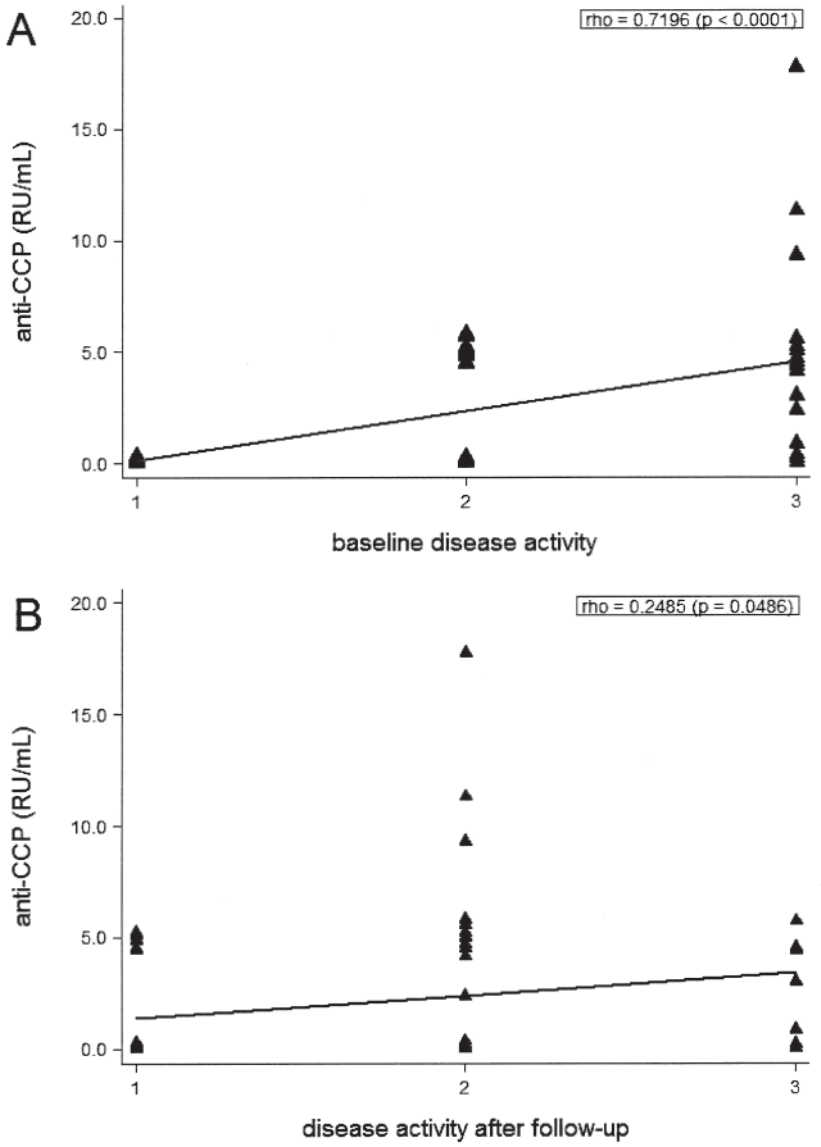

Figure 1. A. Serum concentrations of anticitrullinated protein antibodies (ACPA) in children with juvenile idiopathic arthritis (JIA) according to disease activity at the beginning of the observation (polychoric correlation – rho = 0.72; SE 0.0594; p = 0.0001). B. Serum concentrations of ACPA in children with JIA according to disease activity after followup (polychoric correlation – rho = 0.25; SE 0.0931; p = 0.0486).

After the followup period, 15 out of 36 children with polyarthritis were in Steinbrocker class I, 13/36 were in class II, and 6/36 were in class III. Two out of the group of 9 children with the systemic type of JIA were in Steinbrocker class I, 2/9 were in class II, 4/9 were in class III, and 1/9 was in class IV. Seventeen out of 29 patients with oligoarthritis were in class I, 6/29 were in class II, and 6/29 were in class III (Table 4).

At the beginning of observation, 29 out of 30 children with JIA with low disease activity were classified as class I in the Steinbrocker scale and 1 was in class II. Eleven out of the group of 24 children with JIA with moderate activity were in Steinbrocker class I, 12/24 were in class II, and 1/24 was in class III. Two out of the group of 20 JIA children with high disease activity were in class I, 17/20 were in class II, and 1/20 was in class III (Table 4). A statistically significant higher Steinbrocker score was observed in subjects with a higher disease activity at the beginning of study (rho = 0.71; p = 0.0000001).

After followup, 24 out of 36 children with low disease activity were in Steinbrocker class I, 9/36 were in class II, and 3/36 were in class III. Five out of 28 children with moderate disease activity were in class I, 11/28 were in class II, 11/28 were in class III, and 1/28 was in class IV. Seven out

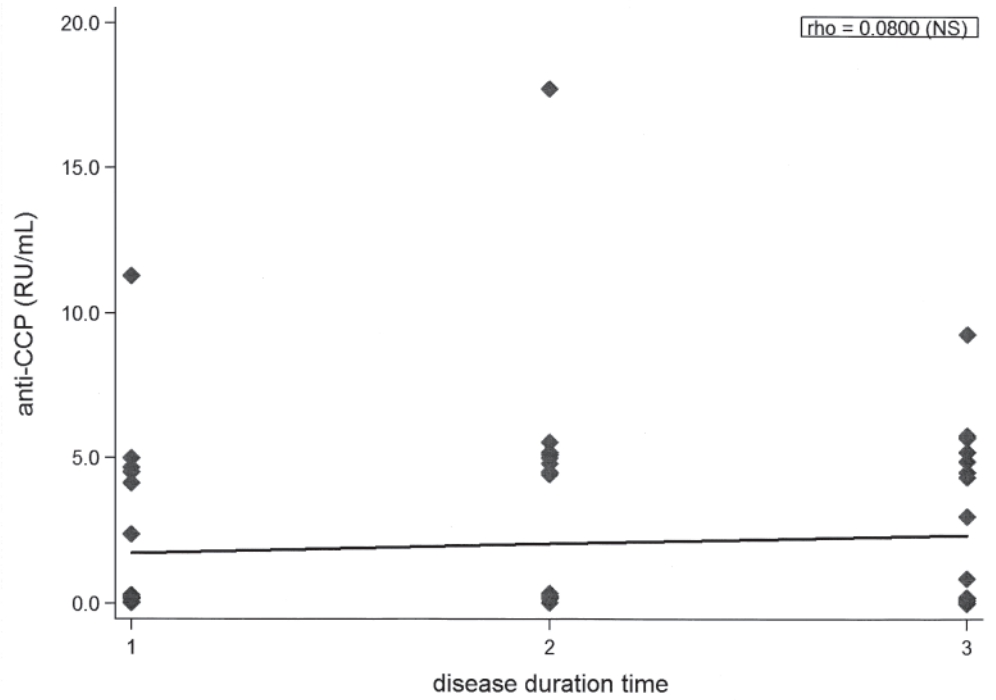

Figure 2. Serum concentrations of anticitrullinated protein antibodies (ACPA) in children with juvenile idiopathic arthritis, according to disease duration time (polychoric correlation – rho = 0.0800; SE 0.1170; p = 0.5326).

Table 4. Radiological status of children with juvenile idiopathic arthritis (JIA) according to JIA onset type, disease activity, and disease duration (total n = 74). Data are n (%).

Steinbrocker scale	I	II	III	IV
At beginning of study	42 (56.8)	30 (40.5)	2 (2.7)	—
After followup	29 (39.2)	20 (27.0)	21 (28.4)	4 (5.4)
Type of JIA onset				
At beginning of study	I	II	III	IV
Polyarticular	24 (66.7)	11 (30.6)	1 (2.8)	—
Systemic	4 (44.4)	3 (33.3)	2 (22.2)	—
Oligoarticular	27 (93.1)	2 (6.9)	—	—
After followup				
Polyarticular	15 (41.7)	13 (36.1)	6 (16.7)	—
Systemic	2 (22.2)	2 (22.2)	4 (44.4)	1 (11.1)
Oligoarticular	17 (58.6)	6 (20.7)	6 (20.7)	—
Disease activity				
At beginning of study	I	II	III	IV
Low	29 (96.7)	1 (3.3)	—	—
Moderate	11 (45.8)	12 (50.0)	1 (4.2)	—
High	2 (10.0)	17 (85.0)	1 (5.0)	—
After followup				
Low	24 (66.7)	9 (25.0)	3 (8.3)	—
Moderate	5 (17.9)	11 (39.3)	11 (39.3)	1 (3.6)
High	_	_	7 (70.0)	3 (30.0)
Disease duration				
At beginning of study	I	II	III	IV
< 6 months	15 (68.2)	7 (31.8)	—	—
6–12 months	19 (61.3)	12 (38.7)	—	—
> 12 months	8 (38.1)	11 (52.4)	2 (9.5)	—
After followup				
< 6 months	10 (45.5)	5 (22.7)	7 (31.8)	—
6–12 months	14 (45.2)	9 (29.0)	7 (22.6)	1 (3.2)
> 12 months	5 (23.8)	6 (28.6)	7 (33.3)	3 (14.3)

of 10 children with high JIA disease activity were in Steinbrocker class III and 3/10 were in class IV (Table 4).

A statistically significant higher Steinbrocker score was noted in JIA children with higher disease activity both at the beginning of the study and after the followup (rho = 0.77; p = 0.0000001; rho = 0.67; p = 0.0000001).

Initially, 15 out of 22 children with JIA with disease duration < 6 months were in Steinbrocker class I, and 7/22 were in class II. Nineteen out of 31 JIA children with disease duration between 6 and 12 months were initially in class I, and 12/31 were in class II. Eight out of 21 JIA children with disease duration time > 12 months were initially in Steinbrocker class I, 11/21 were in class II, and 2/21 were in class III (Table 4).

After the followup, 10 out of 22 subjects with disease duration < 6 months were in class I, 5/22 were in class II, and 7/22 were in class III. Fourteen out of the group of 31 children with disease duration between 6 and 12 months were in class I, 9/31 were in class II, 7/31 were in class III, and 1/31 was in class IV. Five out of 21 JIA children with disease duration > 12 months were in Steinbrocker class I, 6/21 were in class II, 7/21 were in class III, and 3/21 were in class IV (Table 4).

Half of the children presented radiological progression after followup. Radiological progression was observed in the majority of children with JIA with systemic arthritis after followup (8/9), in more than half the children with polyarthritis (20/36), and in 9/29 children with oligoarthritis.

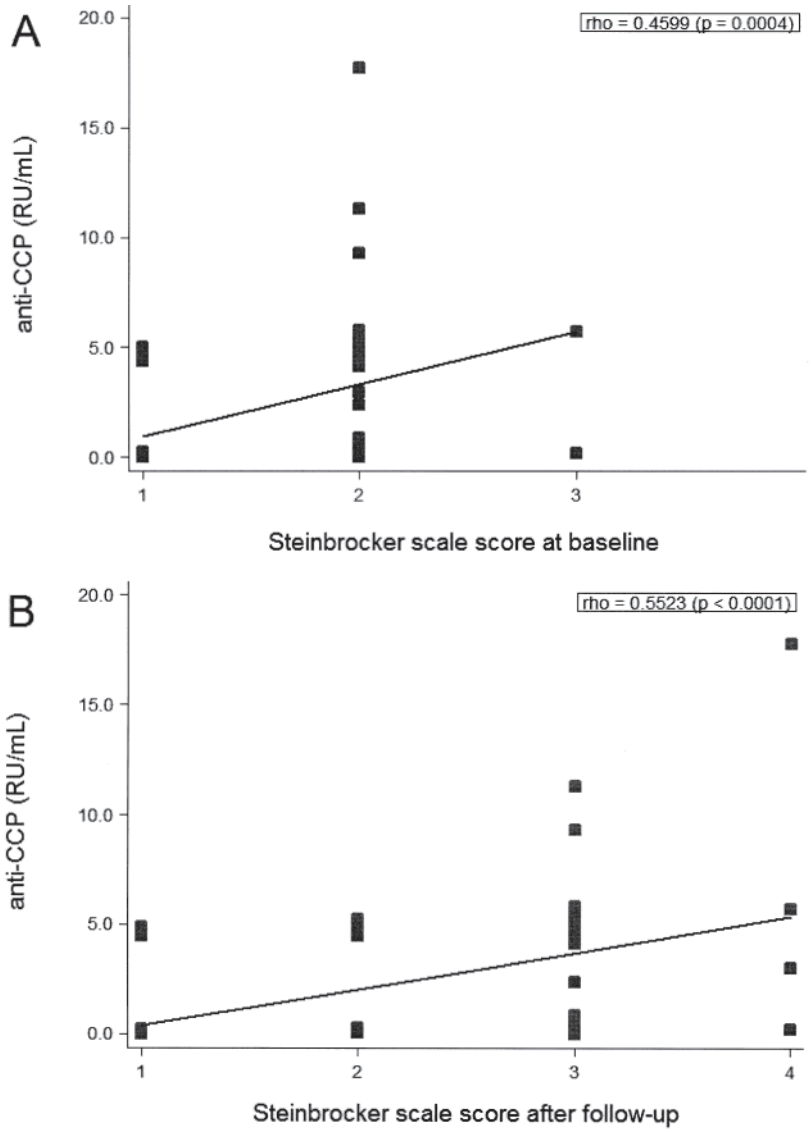

Figure 3. A. Serum concentrations of anticitrullinated protein antibodies (ACPA) in children with juvenile idiopathic arthritis (JIA), according to baseline Steinbrocker scale score (polychoric correlation – rho = 0.46; SE 0.1122; p = 0.0004). B. Serum concentrations of ACPA in children with JIA, according to Steinbrocker scale score after followup (polychoric correlation – rho = 0.55; SE 0.0823; p = 0.0001).

Occurrence of ACPA and radiological status of children with JIA at the study onset and after followup. At the beginning of the study, 6 out of 26 ACPA-positive children with JIA were classified as Steinbrocker class I, 19/26 were in class II, and 1/26 was in class III. After the followup, 3 out of 26 ACPA-positive children with JIA were in class I, 6/26 were in class II, 14/26 were in class III, and 3/26 were in class IV.

Initially, 36 out of 48 ACPA-negative children with JIA were in Steinbrocker class I, 11/48 were in class II, and 1/48 was in class III.

At the beginning of the study, serum concentration levels of ACPA were statistically significantly higher in children from higher radiological Steinbrocker classes (rho = 0.46; SE = 0.1122; p = 0.0004; Figure 3A).

After followup, 26 out of 48 ACPA-negative children with JIA were in Steinbrocker class I, 14/48 were in class II, 7/48 were in class III, and 1/48 was in class IV.

After followup, children with higher serum levels of ACPA demonstrated significantly higher radiological progression (rho = 0.55; SE 0.0823; p < 0.0001; Figure 3B).

Nineteen out of 26 ACPA-positive children with JIA presented radiological progression after the followup compared to 18/48 children who were ACPA-negative.

Additionally, we observed a statistically significant correlation with radiological joint damage (p = 0.0005) in all IgM-RF-positive children with JIA after the followup.

DISCUSSION

According to Ravelli[9], prediction of a longterm outcome soon after JIA onset is difficult because of the heterogeneity of the disease in children and a variety of other reasons, including different assessment methods that complicate comparisons between studies. Thus, while considerable data are accumulating, prediction of the longterm outcome of JIA remains imperfect.

We have shown that a higher serum concentration of ACPA in JIA children is associated with poor clinical outcome of the rheumatoid process, including greater disease activity and erosive disease course, with worse radiological damage in joints. Our analysis revealed predictive superiority of ACPA antibodies over disease activity markers and IgM-RF, findings that are consistent with recent reports concerning predominantly patients with RA[11,29,30].

Until now, only 1 study, by Gilliam, *et al*[16], has evaluated the association of ACPA serum levels with disease severity and radiographic progression in children.

Recent findings indicated the clinical and diagnostic significance of ACPA in adult patients with RA even at a very early stage of the rheumatoid process[11,12,13,14,29,30,31,32,33]. Additionally, ACPA are also present in 20-25% of RF-negative RA cases. Further, the available data show that ACPA could be markers of activity and severity of the rheumatoid process as well as predictors of progressive radiological joint damage[34,35].

In our study group, ACPA were present in 35% (26/74) of children with JIA, a greater frequency than that observed by most other studies (2–10.2%). Numerous authors reported that ACPA were rare in patients with JIA[17,18,19,20,21,22,25,26,36,37]. According to the available data, the frequency of ACPA in children with JIA ranged from 1.8% to 28.6%. The divergence of the results in various reports may be due to different study inclusion criteria and different ACPA cutoff values. Such a high prevalence of ACPA in our investigation might support the results of a study by Low, *et al*[23], who observed ACPA positivity in a wide range from 19.7% to even above 80% in children with JIA, using various epitopes of citrullinated peptides.

In our study group, IgM-RF was found in the sera of only 8% (6/74) of patients with the polyarticular JIA subtype, which is seldom compared to ACPA[2,3]. This observation is consistent with the results of other studies in children with JIA, which stressed rare IgM-RF presence. In our study, all IgM-RF-positive sera were simultaneously positive for ACPA.

We found ACPA-positive cases in all subtypes of JIA. Not surprisingly, half (13/26) of the ACPA-positive children had polyarthritis, since previous studies demonstrated that ACPA were mainly present in patients with IgM-RF-positive polyarthritis, and JIA course was similar to RA[3,21,23,25,26,36,37]. However, in some studies in children with JIA, ACPA were also found in oligoarthritis and systemic JIA, but usually in a lower percentage[18,25,23,26,38]. But in our JIA study group, ACPA were most frequently found in the sera of children with systemic disease (55.5%; 5/9). We observed ACPA mainly in patients with high disease activity and a more aggressive course of the rheumatoid process, with frequent flares and persisting increased acute-phase reactants (e.g., CRP, ESR, PLT); this finding is in agreement with other authors[15,16,17]. As children with systemic JIA were proven to have the highest disease activity, it could be hypothesized that activity of rheumatoid process would affect the ACPA concentration in that group. The concept was also supported by the results in patients with RA[29,39].

Our analysis did not reveal any significant correlation between ACPA level and disease duration. These findings are in line with Miriovsky, *et al*[29] and other studies of patients with RA; however, there are no sufficient data in children with JIA for comparison[11,30,31,32,33,34,35,39,40].

Interestingly, in the subgroup of children with JIA with clinical history between 6 months and 1 year, the presence of ACPA was the lowest. It could be speculated that a large portion of study children with oligoarthritis and low activity of rheumatoid process in that group could explain that observation. Moreover, in that phase (several months after disease onset), a proper treatment is usually implemented and the disease activity tends to decrease. Nevertheless, according to Miriovsky, *et al*[29], changes in ACPA concen-

tration related to RA treatment rarely result in ACPA seroconversion from positive to negative.

Estimation of radiographic progression is essential for a longterm prognosis in patients with rheumatoid process. The prediction of JIA outcome is critical in terms of making proper therapeutic decisions for an individual patient, because modern treatment of JIA requires children to be treated prior to radiographic damage. According to the published data, the rate of structural damage is most rapid early in the disease (especially within the first 2 years), and then gradually decreases to a steady rate[29,41]. In the study by Lindqvist, *et al*[42], the rate of disease progression in patients with RA was found to be 3-fold higher during the first 2 years after study entry compared with subsequent years. Disease duration in children with JIA from our study group was < 2 years — the period of most dynamic disease progression. We demonstrated that children with JIA with high disease activity and longer disease duration presented more severe radiological progression, which is in line with the results obtained by Gilliam, *et al*[16]. Radiological progression after followup was observed in all children with JIA from our study group ($p < 0.05$). The worst radiological destruction was noted in children with JIA with systemic and polyarticular courses of JIA, a finding that supports other authors' results[2,29]. The majority of these children with JIA had more active rheumatoid process than those with oligoarthritis. It is known that IgM-RF is the marker of bad JIA prognosis and that longterm JIA outcome is best in persistent oligoarthritis. The outcome in systemic arthritis is variable, reflecting the heterogeneity of this JIA subtype[2].

All scales assessing radiological status of joints in the course of rheumatoid process were originally designed for adults with RA and are not adequate for assessing growing joints in children with JIA. Many studies aimed to develop adapted versions of the radiographic scoring system for use in JIA[43,44]. The Steinbrocker scale and other radiological classifications have some limitations for the assessment of radiological destruction in JIA and should be modified for more precise use in patients by developmental age. Therefore, besides evaluating new sensitive serological markers such as ACPA, there is a need for alternative imaging techniques (magnetic resonance imaging and ultrasound) that would be more sensitive in detecting early signs of disease activity and joint damage[3,45].

Although data are accumulating on prognostic factors in JIA, prediction of longterm outcome in the first few months remains difficult[2,17,18,19,20,21,22,25,26,36,37]. Greater severity of arthritis at onset, the presence of IgM-RF, and prolonged active disease are not sufficient as predictors of a poor outcome at the disease onset. Although radiographs provide optimal documentation of joint destruction, they are still weaker predictors of severe outcomes than serological markers such as IgM-RF or ACPA in RA. Our study results agree, as we demonstrated that the acute phase indicators as well as disease activity did not differ significantly between ACPA-positive and ACPA-negative children and were consistent with radiological outcomes. In contrast, based on ACPA levels, it was possible to discriminate early between the 2 outcomes as well as to predict the rate of destruction over 2 years.

We observed almost twice as many ACPA-positive children who presented radiological progression after followup compared to the ACPA-negative group. Similar observations were made by Gilliam, *et al*[16], who demonstrated that joint erosion and joint space narrowing were more severe in children with JIA positive for ACPA than in those without ACPA. Further, it was shown that ACPA positivity correlated with signs of radiological destruction even at the beginning of observation.

Since ACPA are thought to even predate the first clinical manifestations of JIA, and because occurrence of these antibodies is believed to be part of the pathophysiological process, the conclusion from our data could be that there might be a subgroup of children with JIA who are already destined to develop erosions even before the first clinical signs of arthritis. Although this statement should be taken with caution because of the relatively small number of patients analyzed, it seems to support other observations made recently in patients with RA[14,46]. The rate of rheumatoid process progression becomes a more important variable in light of the results of several studies in RA, which showed that aggressive treatment could delay joint damage[12,14,46,47].

Syed, *et al*[15] emphasized that the possible usefulness of ACPA in monitoring patients with JIA to determine disease outcome was demonstrated in recent studies. Prognostic markers that identify children with a high risk of more rapid joint damage would provide the justification for applying early aggressive treatment in children with possible extensive destruction within a few years after JIA onset. Kwok, *et al*[17] indicated that ACPA assay could be a valuable tool and a useful predictive test for joint erosion in JIA, particularly in the polyarticular RF-positive subset, and could be helpful in choosing the best therapeutic strategy in patients with recent-onset arthritis. Given the potential toxicity of DMARD and the benefits of early aggressive treatment, prompt identification of patients at greater risk for unfavorable outcomes is important in guiding treatment decisions[48]. Despite the fact that the children in our study were treated with DMARD, the radiological progression was statistically significant compared with baseline radiological status. That could be an argument for an earlier implementation of therapy with biological agents. Nielsen, *et al*[49] provided evidence that biologic agents were capable of reducing the progression of radiographic joint damage based on results in children with JIA, in whom therapy with etanercept was applied. Benucci, *et al*[50] reported similar observations in RA and he demonstrated that anti-tumor necrosis factor-α agents, especially etanercept, reduced disability, disease

activity, and the levels of inflammation indicators. Those data suggest a possible "therapeutic window" early in the course of the disease, during which medical intervention with biologic agents and DMARD could have a more significant effect than treatment given later.

Prediction of longterm outcome in JIA remains imperfect, especially soon after the disease has been manifested. Thus, comparisons among studies are still hindered for a variety of reasons and great effort should be directed toward standardizing the study design and the measurement of predictors and outcomes. We conclude that ACPA are superior to IgM-RF in diagnosing JIA and providing predictive information on the severity of disease course and radiological outcome.

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