

# Proinflammatory S100 proteins as clinical markers of juvenile idiopathic arthritis

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**Objectives.** Proteins of the S100 family (S100A8/9, or calprotectin) are known to be useful disease activity biomarkers of JIA. We hypothesize that titres calprotectin in serum and synovial fluid of children with acute and unconfirmed inflammatory joint symptoms will identify patients who will progress to JIA and our aim is to examine its prognostic value.

**Methods.** A standardized diagnostic evaluation and analysis of serum S100A8/A9 was performed in 115 children with acute (symptoms up to 6 weeks) arthritis as well as in 59 healthy individuals. 47 arthritis patients underwent joint fluid aspiration and samples were collected at the time of presentation. Proteins in serum and synovial fluid were measured by ELISA and compared by the unpaired t test. Arthritis outcome (chronic or transient arthritis) was recorded at 1- and 2-year follow-up periods. JIA diagnosis, disease activity and remission were established according to ILAR and ACR recommendations.

**Results.** The levels of serum and synovial fluid S100A8/A9 were significantly higher in patients with arthritis compared to the levels in healthy individuals ( $p < 0.0001$ ). Serum calprotectin correlated well with disease activity ( $r = 0.539$ ,  $p < 0.05$ ) and the level in synovial fluid ( $r = 0.598$ ,  $p < 0.001$ ). A binary logistic regression model showed that high level of calprotectin predicted chronic arthritis development together with the presence of morning stiffness and higher swollen joint count at the baseline ( $p < 0.001$ ).

**Conclusions.** We have demonstrated that high levels of baseline serum S100A8/A9 (calprotectin) have a prognostic value in predicting a group of patients who following the onset of arthritis will have a chronic disease from those with transient and self-limiting disease.

**Key words:** juvenile idiopathic arthritis, S100 proteins, calprotectin, serum and synovial fluid, outcome, predictors

## INTRODUCTION

Arthritis in children is a group of disorders linked by the clinical signs of persistent joint swelling or painful restriction of joint movement. These fea-

tures may be due to a variety of causes, directly or indirectly caused by an infectious agent, chronic idiopathic, transient or associated with other diseases (autoimmune, autoinflammatory, etc.). It has been estimated that each year ~10/100000 children will develop an inflammatory arthritis (1), most likely juvenile idiopathic arthritis (JIA). The chronic children disease course can be variable, with periods of activity followed by remission. Previous studies

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have shown that up to 70% of children continue to report disability and function's impairment into adulthood (6–8), and with more than one-third of children continuing to have episodes of active inflammation during their adult years (9). A delay in diagnosis, treatment or follow-up may result in joint damage and bone destruction, heart, kidney disease or visual impairment. Identifying early those children who are most likely to have a severe disease course may help to target therapies to those most likely to have poor outcomes and avoid over-treatment in those most likely to experience spontaneous remission (10).

Clinical presentation of JIA is variable. JIA is a heterogeneous disorder comprising several disease subtypes, and these subtypes vary in their demographic characteristics, also clinical, laboratory and joint involvement. Unfortunately, characteristic signs of arthritis often do not develop before the later course of disease, and suitable biomarkers are missing. Consequently, there is a need of biomarkers of progression to chronic disease, which could be used as early as possible in the disease process.

Number and type of joint involvement and associations with antinuclear antibodies (ANA), anti-cyclic citrullinated peptide antibody (anti-CCP), rheumatoid factor (RF) and human leucocyte antigen-B27 (HLA-B27) differ between the JIA subgroups, are not specific and could not be suitable markers for chronic joint disease in children.

S100 calcium-binding proteins are multifunctional proteins that are associated with acute / chronic inflammatory disorders (20). The most familiar S100 proteins, myeloid-related protein S100A8/A9 (calprotectin) have recently been proposed as “alarmins”, which are the endogenous molecules that signal the early phase of tissue and cell damage (1, 14). S100A8/A9 are predominantly expressed by neutrophils, monocytes and activated macrophages (32, 33). Proteins S100A8 and S100A9 form the heterocomplex: S100A8/A9 (calprotectin), which is in an active form. Calprotectin and other members of S100 family are increased locally at sites of inflammation as well as in the circulation of patients with JIA and rheumatoid arthritis (RA) (15–16). Furthermore, a close correlation between S100 proteins and clinical and laboratory markers of disease activity has been demonstrated in patients with different arthritides (16–18). In addition, the expression of S100A8/9 was found to be strongest at the cartilage–pannus junc-

tion, so there is evidence for release of this protein in the synovial fluid obtained from inflamed joints (15). S100A8/A9 is known as a good biomarker for local inflammation in affected joints, and as a clinical marker of disease activity in patients with RA and JIA. Unlike adults affected by rheumatoid arthritis, children with JIA have a significant chance to recover completely in adolescence (11–12).

There is evidence that therapeutic intervention early in the disease course of juvenile idiopathic arthritis in children leads to earlier disease control and less joint damage (5).

We hypothesized that titres of S100A8/A9 (calprotectin) in serum and synovial fluid of children with acute and unconfirmed inflammatory joint symptoms will identify patients who will progress to JIA and our aim is to examine its prognostic value.

## MATERIALS AND METHODS

**Patients.** From 2010 to 2014, following an informed consent, patients with acute arthritis were enrolled at the Children Hospital, Affiliate of Vilnius University Hospital Santariškių Clinics, and were followed up for as long as 2 years. Acute arthritis cohort comprises 115 patients (of which 47 had synovial fluid samples). The study was approved by the Bioethics Committee of Lithuania (Registry 2012-01-11 No. 158200-01-444-125). Participation in the study was voluntary, before entry into the protocol each patient gave a written consent after receiving verbal and written information. Patients inclusion criteria in an acute arthritis cohort were as follows: (1) age <16 years, (2) confirmed presence of arthritis (joint pain, swelling or reduction of joint mobility) in at least 1 joint if the symptoms lasted <6 weeks. Other causes of arthritis were excluded. None of the patients had been receiving disease-modifying anti-rheumatic drugs (DMARDs), glucocorticoids (GCs) or biologic therapy at the baseline. The control group consisted of 56 healthy individuals without acute or chronic inflammation and arthralgia.

**Baseline assessment.** A standard rheumatologic evaluation was performed at the first visit. The demographic and clinical data were recorded. Probable diagnostic variables were age, gender, duration of symptoms at the first visit, joint counts, duration of morning stiffness, disease activity score. Disease activity was assessed using the standard American College of Rheumatology (ACR) core set (Table 1).

**Table 1.** JIA disease activity core variables (ACR<sup>1</sup> recommendations)

1. Physician global assessment of overall disease activity (VAS<sup>2</sup>; range 0–100 mm)
2. Parent or patient global assessment of overall well-being (VAS; range 0–100 mm)
3. Functional ability (CHAQ)
4. Number of joints with active arthritis
5. Number of joints with limited range of motion
6. Index of inflammation: ESR or CRP

<sup>1</sup> ACR – American College of Rheumatology;

<sup>2</sup> VAS – Visual Analogue Scale.

Blood samples were taken for routine diagnostic laboratory testing (erythrocyte sedimentation rate (ESR), C reactive protein (CRP), antinuclear antibody (ANA) positivity, presence of human leucocyte antigen (HLA) B27, infectious serology screening) and stored to measure other serum markers (among others calprotectin (S100A8/9)) subsequently. The samples of synovial fluid (SF) were obtained from 47 patients with knee effusion according to the national treatment protocol. Control samples of SF were obtained from 17 children undergoing arthroscopy and arthrocentesis for orthopaedic pathologies without symptoms of local infections or systemic diseases.

**S100A8/9 ELISA.** Blood and synovial fluid samples were collected at the baseline and 171 serum (115 patients with arthritis and 56 healthy control children) and 64 synovial fluid (47 arthritis and 17 healthy control patients) samples were available for analysis. Serum and SF samples were immediately centrifuged and stored at –80 °C until the analysis. The levels of serum S100A8/9 (BioLegend Inc, San Diego, USA) were measured by using commercially available ELISA kits according to the manufacturer's instructions. The sensitivities of the assay were  $0.62 \pm 0.34$  ng/ml.

**Follow-up assessment.** All the patients with acute arthritis (symptoms duration up to 6 weeks) according to clinical and laboratory evaluation at the baseline were categorized into 2 groups of diseases: infectious (or reactive arthritis) and acute (idiopathic) arthritis. 6 patients with confirmed conditions such as osteochondritis dissecans, leukemia, systemic lupus erythematosus (SRV) or other vasculitis were not followed up further. At the 6th month, 1- and 2-year follow-up periods, 109 patients (from 115 acute arthritis cohort excluded 6 patients with confirmed other diseases) were evaluated by the rheumatologist, who measured the disease activity

score and were assessed on two outcomes. First, diagnosis of JIA (chronic arthritis) was considered at the 6th month of symptoms duration according to the International League of Associations for Rheumatology (ILAR) criteria. Persistent or chronic arthritis was defined as the presence of arthritis in at least 1 joint and / or treatment with DMARDs or steroids or biologic therapy within the 6th month at 2-year follow-up. Second, patients with transient arthritis (TrA) were free of symptoms and in natural remission at follow-up periods.

**Statistical analysis.** The concentrations of S100 proteins as quantitative variables were expressed as means, median and dispersion parameters. The Kolmogorov-Smirnov test of normality was performed for all variables and their difference scores. Pearson's correlation coefficients and Spearman's rank correlation coefficients were used in the cases of normal and non-normal variables, respectively. To compare different groups, the independent samples *t*-test was used for normal variables and the Mann-Whitney *U* test was used as a nonparametric alternative. Association between baseline factors and ultimate diagnosis of JIA (yes / no) were assessed by the multivariate logistic regression model. The results are presented as odds ratios (OR) with 95% CIs. For all statistical evaluations, *p* values below 0.05 were considered to be statistically significant. Statistical analyses were performed using SPSS version 20.0 (SPSS Inc. Chicago, IL, USA).

## RESULTS

Table 2 shows the baseline characteristic of the patients and healthy controls. Of the 109 patients included, after 1 year of follow-up 41 developed JIA, 68 evolved inactive disease or natural remission (transient arthritis) (at the baseline 6 patients were diagnosed with other pathologies (leukemia,

**Table 2.** Baseline characteristics of patients with acute arthritis and healthy controls

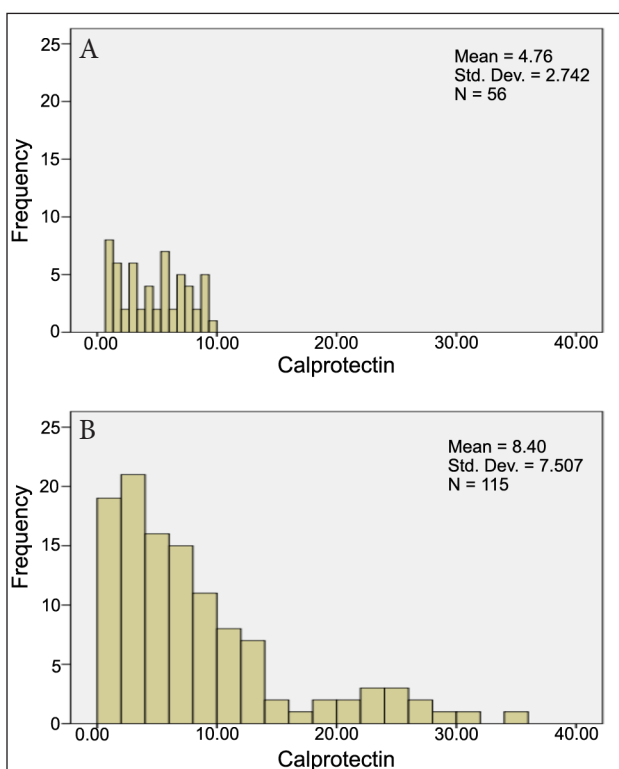
Characteristic	Acute arthritis patients (n = 115)	Healthy controls (n = 73)
Mean age, years ( $\pm$ SD)	8.09 ( $\pm$ 4.87)	10.16 ( $\pm$ 3.70)
Gender, F/M	65/50	24/49
Mean ESR, mm/h ( $\pm$ SD)	20.70 ( $\pm$ 21.16)	320 ( $\pm$ 2.31)
Mean CRP, mg/L ( $\pm$ SD)	15.32 ( $\pm$ 27.23)	2.61 ( $\pm$ 11.25)

ESR – erythrocyte sedimentation rate; CRP – reactive protein.

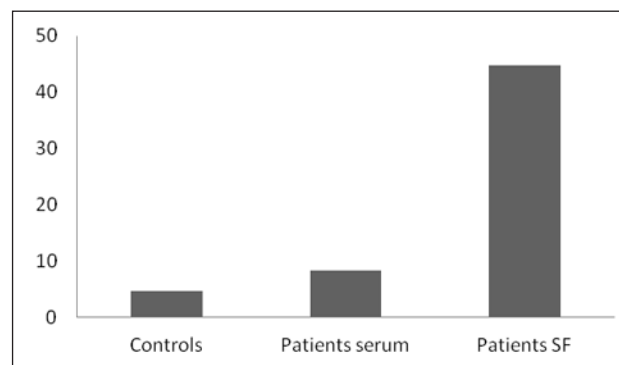
systemic lupus erythematosus, other vasculitis and orthopedic conditions) and were not followed up then). At 2 years of the follow-up period 6 patients were lost to follow up, 33 still had active disease or were treated with antirheumatic drugs (DMADRs, biologic, corticosteroid therapy) and 70 patients were in remission or inactive disease.

The levels of serum S100A8/9 (calprotectin) (mean  $8.4 \pm 7.51$   $\mu$ g/ml) were significantly higher in patients with acute arthritis compared with healthy controls (mean  $4.76 \pm 2.74$   $\mu$ g/ml,  $p > 0.001$ ) (Fig. 1). The mean of calprotectin concentration in synovial fluid was  $45.51 (\pm 108.02)$   $\mu$ g/mL, marked significantly higher than in healthy

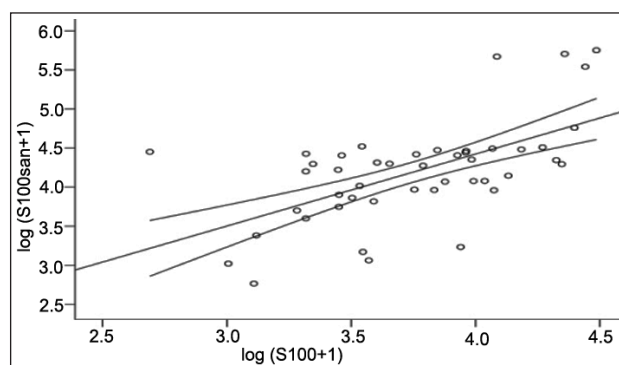
controls SF (mean  $0.02 \pm 0.01$   $\mu$ g/mL) and to 5–30 fold higher than in serum (Fig. 2). A strong correlation between calprotectin serum concentration and concentration in SF ( $r = 0.598$ ,  $p < 0.001$ ) was observed in individual patients (Fig. 3).



**Fig. 1.** Calprotectin (S100A8/9) distribution ( $\mu$ g/ml) in (A) healthy controls and (B) patients with acute arthritis cohort



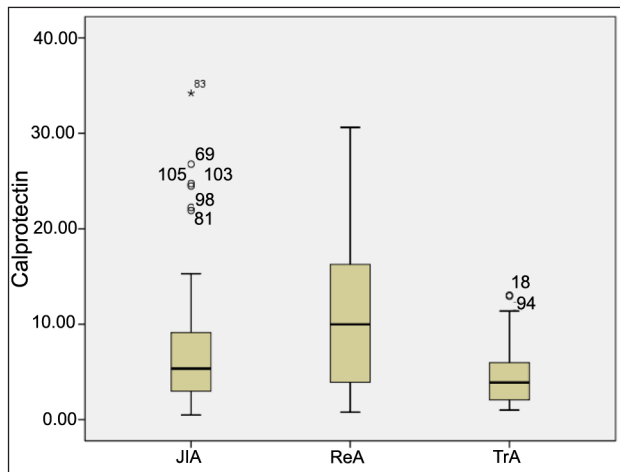
**Fig. 2.** S100A8/A9 (calprotectin) levels in healthy controls and patients with acute arthritis in serum and synovial fluid (SF) ( $\mu$ g/ml)



**Fig. 3.** Scatterplots showing correlations between acute arthritis patients' serum and synovial fluids levels of S100A8/9 (calprotectin)

After thorough clinical and laboratory investigation at the baseline, patients with acute arthritis were classified according to international criteria into three categories: JIA (n = 50, 45.9%),

reactive (n = 36, 33%) and undifferentiated arthritis (n = 23, 21.1%) (Fig. 4). Patients with reactive arthritis had significantly higher calprotectin serum levels (mean  $11.23 \pm 8.46 \mu\text{g/mL}$ ) than patients with undifferentiated arthritis (mean  $4.97 \pm 3.78 \mu\text{g/mL}$ ,  $p < 0.002$ ), and not significantly but higher than JIA patients' serum calprotectin (mean  $7.84 \pm 7.57 \mu\text{g/mL}$ ,  $p = 0.054$ ). We found significantly higher levels (around 50-fold higher) of the baseline S100A8/A9 level in synovial fluid in patients with reactive arthritis compared with



**Fig. 4.** Serum calprotectin levels ( $\mu\text{g/ml}$ ) compared in patients with primal diagnoses at baseline ( $p = 0.011$ ). JIA – juvenile idiopathic arthritis; ReA – reactive arthritis; TrA – transient arthritis.

JIA patients ( $p < 0.032$ ) and undifferentiated arthritis ( $p < 0.012$ ).

109 patients with acute arthritis had the following disease outcome at 1 follow-up: chronic arthritis or JIA (37.6%) and transient arthritis (62.4%). Table 3 shows the main clinical factors associated with JIA progression. In the univariate analysis, the calprotectin serum levels of JIA patients correlated positively with ESR ( $r = 0.530$ ,  $p = 0.02$ ), CRP ( $r = 0.447$ ,  $p = 0.003$ ), physician's disease activity score ( $r = 0.343$ ,  $p = 0.032$ ) and strong significant correlation was determined with articular calprotectin ( $r = 0.682$ ,  $p < 0.0001$ ), meanwhile serum calprotectin level of transient arthritis did not correlate with articular calprotectin completely ( $p = 0.22$ ).

At the first visit, clinical and laboratory parameters were selected to discriminate between chronic (JIA) arthritis and transient arthritis. Baseline characteristics of JIA patients associated with chronic arthritis are presented in Table 4. The strongest association with chronic arthritis was seen for the higher affected joint count at the first visit, presence of morning stiffness and longer symptoms duration ( $>4$  weeks). High levels of ESR and calprotectin at the baseline also showed a strong association with chronic arthritis. Gender and age did not influence JIA development in the acute arthritis cohort. Similarly, the CRP level was not an important predictor of JIA development.

**Table 3.** Clinical factors associated with JIA progression

Variable	JIA (n = 41)	TrA (n = 68)	p value
Age, years	7.90 (1–16)	8.15 (1–16)	0.648
Gender (F/M)	27/14	32/36	0.058
Symptoms duration to 1 week (n, %)	7/17.1	21/30.9	<b>0.001</b>
Presence of morning stiffness (yes/no)	33/8	31/37	<b>0.001</b>
Number of swollen joints (range)	6.4 (1–40)	2.6 (1–14)	<b>0.001</b>
ANA (yes/no)	19/22	12/56	<b>0.001</b>
HLA B27 (yes/no)	16/25	23/45	0.330
ESR (range)	25.8 (0–93)	17.3 (0–73)	<b>0.032</b>
CRP (range)	19.1 (0–149)	10.8 (0–119)	<b>0.001</b>
Serum calprotectin, $\mu\text{g/ml}$	10.66 (0.79–34.2)	6.96 (0.49–30.6)	<b>0.001</b>
Pain, mm	50.3 (12–95)	50.6 (0–100)	0.981
PGA, mm	43.6 (0–90)	38.8 (0–100)	0.360
CHAQ (range)	0.78 (0–2.250)	0.66 (0–2.625)	0.165
DAS	4.6 (0.5–9)	3.5 (0.5–7)	<b>0.026</b>

Bold shows significant p value. JIA – juvenile idiopathic arthritis; TrA – transient arthritis; ANA – antinuclear antibodies; HLA B27 – human leukocyte antigen B27; ESR – erythrocyte sedimentation rate; CRP – C reactive protein; PGA – patient global assessment; CHAQ – children health assessment questionnaire; DAS – disease activity score.

**Table 4.** Baseline characteristic of patients with acute arthritis in relation to outcome measures: JIA development

Clinical variables	OR (95%)	p value
Morning stiffness (presence)	4.92 (1.99–12.21)	0.001
Symptoms duration (>4 weeks)	4.58 (1.68–12.5)	0.003
Affected joints (>5)	5.03 (1.84–13.78)	0.002
Poliarthrititis (versus oligoarthritis)	3.58 (1.43–8.99)	0.007
Calprotectin (>5.79 µg/mL)	3.08 (1.36–6.96)	0.007
ESR (>10 mm/h)	3.66 (1.25–10.72)	0.018

The variables significantly associated with the JIA diagnosis in the univariate analysis (calprotectin, presence of morning stiffness, higher affected joint count, polyarthritic joint involvement, ESR) were further examined in a multiple binary logistic regression analysis for prediction of JIA. The model showed that a high level of calprotectin easier predicted chronic arthritis development together with the presence of morning stiffness and higher swollen joint count at the baseline ( $p < 0.001$ ). This model predicts 72.7% true cases. Positive antinuclear antibodies (ANA) showed the strongest association (OR 20.89 (3.71–117.58),  $p > 0.001$ ) with JIA at an early stage of disease (6 month follow up), and did not influence chronic disease at 1 and 2 years of follow-up.

## DISCUSSION

In this study we have shown for the first time significantly increased serum levels S100A8/9 (calprotectin) in children with acute arthritis (symptoms duration up to 6 weeks), not specified disease, who had not yet been exposed to standard treatment. Our data indicate that patients with acute arthritis had significantly higher concentrations of calprotectin in serum and synovial fluid compared with healthy children. S100A8/A9 acts as proinflammatory cytokines based on their high extracellular expression in the inflamed joint by activated immune cells (33).

The S100A8/A9 heterodimer has been shown to be a reliable indicator of disease activity and joint inflammation in continued inflammatory rheumatic diseases, including RA (2, 17), JIA (18, 19, 21), psoriatic arthritis (22), and spondyloarthropathy (23). Past reports showed elevated circulating S100 proteins in patients with previously established JIA disease (17, 19, 20) and suggested that patients with clinically inactive JIA but elevated S100A8/A9 may be at risk for disease flares (20). Calprotectin has

recently been demonstrated to predict 10-year radiographic progression in patients with established rheumatoid arthritis (2).

The high expression of calprotectin in infiltrating monocytes and neutrophils in synovial fluid is due to release of these proteins at sites of inflammation (19). It is evident that S100 proteins are broadly produced by activated immune cells of the synovial membrane and synovial fluid in affected joints and pass into the blood circulation (3). Our data showed that children with acute arthritis had around 10–20 times higher levels of S100A8/A9 in synovial fluid compared with serum and showed a good correlation of SF and serum in individual patients. However, in this study, we have shown significantly increased serum levels of calprotectin in patients with reactive arthritis also, especially in synovial fluid. Several patients with established reactive arthritis showed elevated SF calprotectin by 50 times higher compared with serum.

Obviously, high serum concentrations indicate local inflammation rather than systemic activation of the immune system. It is defined that S100A8/A9 induction in macrophages is Il-10-dependent therefore this protein has anti-inflammatory properties and may be crucial for the protection against bacterial infection (24). Il-10 is responsible for the suppression of Th-1-like cytokines including IFN- $\gamma$  and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). These cytokines are necessary for the elimination of bacteria associated reactive arthritis. In patients with reactive arthritis, Il-10 is present at high amounts within the synovial fluid upon stimulation with bacterial antigens (15).

S100A8/A9 showed good correlations with several clinical markers of disease activity. Compared to previous studies, the levels of calprotectin measured in our study showed a better correlation with ESR nor CRP, as demonstrated in different researches (2, 22, 26). As well, CRP poorly correlated with other disease activity parameters. CRP is mainly influenced by systemic involvement and

provides very little information about local inflammation (19), whereas S100 proteins are performed and released immediately upon activation of the particular immune cells population at the local site of inflammation (18). Also, our data showed a significant association of calprotectin with a high number of affected joints ( $p = 0.032$ ) most likely due to major involved synovial tissues damage.

We assessed a potential role of S100A8/A9 protein as a predictive biomarker of chronic disease. By analyzing patient's follow-up data we looked for the factors influencing chronic arthritis outcome. Comparing two groups (JIA and transient arthritis) at the one year follow-up period we found some differences of symptoms at the baseline. Patients who developed JIA (chronic disease) during the acute phase of disease were significantly associated with a higher number of swollen joints, presence of morning stiffness, antinuclear antibodies (ANA), ESR, CRP, serum calprotectin and physician's global assessment tool. The search of predictive factors of arthritis outcome has been the subject of many studies. Most of studies analyzed the outcome and poor prognosis in selected patients with already established JIA (10, 27–29). We can report similar findings: presence of morning stiffness, high number of swollen joints and acute phase reactants (ESR and CRP) at an early stage of disease are commonly reported as JIA or RA poor outcome risk factors.

It is important to note that high concentration of S100A8/A9 is strongly associated with development of JIA. We can suggest that very high disease activity at the baseline may predict chronic disease development afterward. In our study about 50% patients with the established reactive arthritis diagnosis and very high calprotectin concentration at the baseline fulfilled the JIA criteria according to ILAR recommendations after 1 year of follow-up. Human leucocyte antigen B27 (HLAB27) was not significant for increased risk of developing JIA in our cohort. For children and adolescents less than 16 years of age, the International League of Associations for Rheumatology recently proposed to classify childhood reactive arthritis under the umbrella of JIA, as enthesitis-related arthritis (30). All our patients with primal reactive arthritis who developed chronic disease at the follow-up were diagnosed with enthesitis-related JIA (data not shown). The role of infection for chronic arthritis is still not

clear. Components of triggering bacteria including nucleic acids and proteins have been identified in the synovium and in circulatory monocytes of patients with rheumatoid arthritis (25). Clinically, the duration of reactive arthritis for more than 6 months is already the sign of development of chronicity (31). But at the early stage of disease, according to our data, high calprotectin level in acute arthritis could be associated with JIA development despite of detected infectious markers at the early stage of disease. The process of JIA development and the role of infection are unclear until now.

These predictive values could point to the line from which therapeutic decisions can be made in an early phase of the arthritis. The early recognition of chronic arthritis allows early intervention with DMARDs, which will lead to earlier disease control and improvement of disease outcome (4). Otherwise, early recognition of self-limiting arthritis will prevent unnecessary treatment of these cases with potentially toxic DMARDs.

## CONCLUSIONS

We have demonstrated that high levels of baseline serum S100A8/A9 (calprotectin) have a prognostic value in predicting a group of pediatric patients who following the onset of arthritis will have a chronic disease from those with transient and self-limiting disease. Routine collection of serum to assess calprotectin concentration could be an essential option to start conventional therapy or to avoid giving unnecessary and expensive treatment.

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#### **UŽDEGIMĄ SKATINANTIS BALTYMAS S100A8/A9 (KALPROTEKTINAS) – SVARBUS JAUNATVINIO IDIOPATINIO ARTRITO LIGOS AKTYVUMO IR PROGNOZĖS BIOŽYMUO**

*Santrauka*

**Įvadas.** S100 baltymų šeima – uždegimą skatinančios, gausiai neutrofilų, monocitų ir aktyvuotų makrofagų ekspresuojamos medžiagos, dalyvaujančios artritų pato-

genezėje. Geriausiai yra žinomas baltymas S100A8/A9 (kalprotektinas), kuris randamas sinoviniame skystyje, seilėse, išmatose ir kraujo serume. Suaugusiems, kurie serga reumatoidiniu artritu, S100 baltymai naudojami kaip lėtinio uždegimo aktyvumo biožymuo. Darbo tikslas – nustatyti, ar vaikams su ūmiu artritu kalprotektino koncentracijos pokyčiai kraujo serume ir sąnariname skystyje gali prognozuoti JIA vystymąsi.

**Metodika.** Ištirta 115 vaikų (iki 16 metų amžiaus) su ūmaus artrito (simptomai iki 6 sav.) klinika bei 59 sveiki vaikai, nesergantys lėtinėmis ar ūminėmis uždegiminėmis ligomis. Pirmojo vizito metu ligoniams atlikti kliniškinis ir laboratorinis tyrimai, surinkti kraujo serumo ir sąnarinio skysčio (47 ligonių) mėginiai. Kalprotektino koncentracija nustatyta imunofermentiniu ELISA rinkiniu. Ligonių būklės vertintos 2 metus (periodai: po 6 mėn., po 1 ir 2 metų). Tiriant ligonius su ūminiu artritu ir taikant logistinės regresijos modelį nustatyti reikšmingi lėtinės ligos (JIA) progresavimo kriterijai.

**Rezultatai.** S100A8/A9 (kalprotektino) koncentracija tiek kraujo serume, tiek sąnariname skystyje buvo ženkliai didesnė ligoniams su ūminio artrito klinika, palyginti su kontrolinės grupės vaikais ( $p < 0,0001$ ). Kalprotektinas serume gerai koreliavo su sąnarių ligos aktyvumu ( $r = 0,539$ ,  $p < 0,05$ ); kalprotektino koncentracija sąnariname skystyje ( $r = 0,598$ ,  $p < 0,001$ ). S100A8/A9 reikšmingai didesnė ligonių su reaktyviu artritu (daugumai po 6 mėn. išsivystė JIA). Remiantis binarine logistinės regresijos analize analizuojant kiekvieną ūminio periodo kintamąjį atskirai, nustatyti lėtinės ligos prognostiniai žymenys po 1 metų: kalprotektino koncentracija  $>5785$  ng/ml (ŠS 4,372 [1,59–12,017]), sąnarių skaičius  $>5$  (ŠS 8,677 [2,149–35,038]), rytinis sąnarių sustingimas  $>15$  min. (ŠS 6,299 [1,996–19,881]) ( $p < 0,001$ ).

**Išvados.** S100A8/A9 (kalprotektino) didelės koncentracijos ūmioje ligos stadijoje puikiai koreliuoja su uždegimo aktyvumu ir gali prognozuoti lėtinio artrito vystymąsi.

**Raktažodžiai:** jaunatvinis idiopatinis artritas, S100 baltymai, kalprotektinas, serumas ir sinovinis skystis, būklė, prognostiniai žymenys