

RESEARCH ARTICLE

Atopy in children with systemic onset juvenile idiopathic arthritis (SoJIA) is associated with a worse outcome

Wen-Ming Zhang, Ling-Yun Xu, Yan-ming Lu, and Lan-Fang Cao

Department of Pediatrics, Renji Hospital Affiliated to Shanghai Jiao-Tong University School of Medicine, Shanghai, China

Abstract

Context: Atopy and systemic onset juvenile idiopathic arthritis (SoJIA) are two potential outcomes of a dysregulated immune system. Although rare, SoJIA causes 60% of the morbidity of JIA patients which exhibit a wide heterogeneity of prognosis and treatment. Co-morbidities can complicate the responses to therapy.

Objective: To study the influence of co-existing atopy on the prognosis of SoJIA.

Materials and Methods: Patients diagnosed with SoJIA between Jan 2006 and Sep 2010 were screened, enrolled in this prospective cohort study, and followed for 2 years. Management of SoJIA patients was assessed by ACR Pedi30/50/70 criteria, laboratory variables, and systemic feature score.

Results: At disease onset, 61 SoJIA patients (34 male and 27 female) were enrolled and were divided into SoJIA patients with atopy ($n = 27$) or those without atopy ($n = 34$). Atopic group at disease onset had significantly higher numbers of affected joints, ferritin levels and IgE serum levels than the non-atopic group. At 3 and 6 months, fewer SoJIA patients with atopy reached the ACR Pedi50 criteria ($p < 0.02$). During the 2 years of follow-up time, the number of infections and the number of flares were significantly higher in the SoJIA with atopy group ($p < 0.01$).

Conclusion: Atopy may exert an adverse influence on SoJIA, as patients with atopy had a more active disease at diagnosis and poorer outcome. This prospective study showed that the TH1/TH2 hypothesis was too simplistic to explain the interaction between atopy and SoJIA.

Keywords

Atopy, autoimmunity prognosis, infection, risk factor, systemic onset juvenile idiopathic arthritis

History

Received 13 November 2013

Revised 20 February 2014

Accepted 21 February 2014

Published online 10 March 2014

Introduction

Systemic onset juvenile idiopathic arthritis (SoJIA), a chronic, inflammatory joint disease, accounts for approximately 4–20% of cases of juvenile idiopathic arthritis^{1–3}. SoJIA is characterized by spiking fevers, an evanescent macular erythematous rash, arthritis in at least one joint for six or more weeks, and one or more additional extra-articular features, such as anemia, hepatosplenomegaly, lymphadenopathy, leukocytosis, thrombocytosis and serositis^{3,4}. SoJIA can entail frequent relapses of disease activity, a long disease course that extends into adulthood, and long-term treatment⁵. SoJIA patients exhibit a wide heterogeneity of symptoms and responses to therapy^{1,6,7}, and their treatment regimen is based on recommendations by the American College of Rheumatology¹. Abnormalities in the innate immune response play a significantly more prominent role in pathogenesis of SoJIA compared to other subtypes of JIA, where abnormalities in the adaptive immune response play a role^{8,9}. These data suggest that SoJIA is an autoinflammatory, rather than an autoimmune disease.

Atopy usually appears during early childhood and affects approximately 5.8% to 63.9% of children¹⁰. Atopy is diagnosed based on both clinical symptoms (hay fever, allergic asthma, allergic eczema and neurodermatitis) and at least two positive laboratory tests or abnormal dermatologic responses¹¹. Pathologic features of atopic disorders consist of elevated IgE serum concentrations, elevated Th2 type cytokines (interleukin 4 (IL-4), IL-5, IL-13), and specific responses to more than one environmental proteins in a Skin Prick Test (SPT) or a Radio Allergo Sorbent test (RAST)¹¹. Atopy is thought to result from exposure to aero-allergens which promote the differentiation of T helper (Th) cells towards Th2 cells and induction of B lymphocytes to produce specific IgE against the allergens. Th2 responses are thought to reduce the maturation of Th1 responses. Th1 cells appear involved in JIA¹², although their role appears to be less prominent in SoJIA than cells of the innate immune response, including macrophages^{8,13,14}.

Allergic conditions are thought to protect against the onset of autoimmune diseases or modulate their severity, due to the dichotomy of the association of the overactive T helper type 2 (Th2) lineage with allergic manifestations and association of overactive Th1 with several autoimmune diseases¹⁵. However, neither antagonism nor synergism was detected between the presence of atopy and autoimmune diseases in a large survey

Address for correspondence: Lan-Fang Cao, Department of Pediatrics, Renji Hospital Affiliated to Shanghai Jiao-Tong University School of Medicine, No. 160 Pujian Road, Shanghai, 200001, China. Tel: +86 2153882035. Fax: +86 2153882035. E-mail: clf530417@126.com

of adults¹⁶. Likewise, type I diabetes did not significantly affect the incidence of allergic symptoms¹⁷. Paradoxically, highly elevated IgE serum concentrations significantly increased the risk for eventual development of autoimmune diseases¹⁸.

Atopy and autoimmune/autoinflammatory diseases are immunopathologic conditions that involve both chronic inflammation and hypersensitivity to exogenous and endogenous antigens, respectively. Corticosteroids are used in treatment of both diseases. Both atopy and SoJIA are associated with low Natural Killer cytotoxic function^{19,20}, higher numbers of Th17 cells and elevated IL-17 levels^{11,12,21}. Macrophage activation syndrome is associated with SoJIA and high ferritin levels, but not atopy^{3,14}. Atopy is characterized by high levels of Th2 cytokines¹¹ while SoJIA is characterized by high IL-1, IL-6, and TNF- α proinflammatory cytokines³.

The effects of co-existing atopic disease and/or their treatments on SoJIA disease activity or prognosis remain unknown. In this study, we aimed to assess the influence of atopic diseases on children with SoJIA.

Patients and methods

Patients

SoJIA patients were diagnosed by a rheumatologist using the criteria for the JIA issued by ILAR, 2001²² at Renji Hospital from Jan 2006 to Sep 2010. Consecutive SoJIA patients were invited to enroll. Exclusion criteria were infectious disease, leukemia, lymphoma and other connective tissue diseases. Ethics committee approval for this prospective study was obtained at Renji Hospital, which is affiliated to Shanghai JiaoTong University School of Medicine. Written, informed consent was obtained from the parents and children.

The patients were assessed by our rheumatologist monthly during the trial. A standardized data collection protocol was used for all patients to record demographics (age, sex), individual and family histories (first and second degree relatives) of atopy, clinical JIA symptoms (systemic feature score: fever, rash, lymphadenopathy in cervical, axillary, inguinal regions, hepatomegaly, splenomegaly, and serositis; joints with active disease), patients' complete treatment history (six months post disease onset), and laboratory data (erythrocyte sedimentation rate (ESR), platelet (PLT), C-reactive protein (CRP), ferritin, specific IgE concentrations). Each of eight systemic features was given a score of 1 (present) or 0 (absent): fever; rash; lymphadenopathy in cervical, axillary, and inguinal regions; hepatomegaly; splenomegaly; and serositis. A summary score indicated the number of features present (range 0–8)²³. Assessment of the arthritic involvement included number of inflamed joints (the numbers of swollen/effused joints, or joints having at least 2 of the following features: heat, limited range of movement, and tenderness/pain on range of movement).

Atopy diagnosis had been recorded previously²⁶. Briefly, the atopic patients had positive serum specific IgE concentrations (>0.70 kU/l), SPT results or individual and family history of atopy (at least 2 of them were positive was regarded as atopy). Additional variables including infection times, results of SPT, RAST were also recorded.

Criteria for SoJIA improvement

Improvements were scored according to the criteria of the American College of Rheumatology Pediatric 30% (ACR Pedi 30), ACR Pedi 50 and ACR Pedi 70. Briefly, an ACR 30, ACR 50, ACR 70 improvement indicated that at least 3 of 6 ACR Pedi variables improved by at least 30%, 50% or 70%, respectively, and no more than one variable worsened by more than 30%. The ACR Pedi variables were physician's and patients'/parents' global assessment on a 10 cm visual-analogue scale; functional ability (childhood health assessment questionnaire CHAQ); number of active joints defined by the presence of swelling, restricted motion accompanied by pain or tenderness or both; number of joints with restricted movement; and ESR.

Laboratory tests

Specific IgE antibodies directed against inhaled allergen including dust mites, mold, pollen, herbs, cockroach, latex, cat and dog hair, and food allergen including milk, eggs, crabs, and shrimp were measured with Allergen ImmunoCAP using the Pharmacia UniCAP System. The cut-off IgE level was 0.35 kU/l and values >0.70 kU/l represented a positive result. Serum total IgE was measured by nuclear medicine laboratory in Renji Hospital with chemical luminous method. Standard laboratory tests performed at Renji Hospital measured the C-reactive protein (CRP), eosinophil cationic protein (ECP), erythrocyte sedimentation rate (ESR) and ferritin.

Skin prick test

All patients had undergone a SPT with a standardized procedure. Briefly, the volar surface of the non-dominant side forearm was injected in a grid pattern with a standard panel of airborne allergen extracts, including the Ga2len Pan-European Standard SPT Panel, sterile saline (0.9%; a negative control) and histamine (10 mg/ml saline; a positive control). After 15 min, one of two experienced blinded allergy nurses assessed the SPT results: two wheal diameters at perpendicular angles were measured and expressed as the mean. A positively scored wheal diameter was ≥ 3 mm larger than the negative control.

Follow-up

After two-year follow-up period, we classified the disease course of the SoJIA patients as monophasic, polycyclic or persistent. Polycyclic disease was defined as alternating periods of active disease and inactive disease for any period of time and then recurrence of active disease²⁴. Patients have "inactive disease" if they simultaneously meet all of the following criteria: (1) No joints with active arthritis (using the American College of Rheumatology definition of "active joint"); (2) No fever, rash, serositis, splenomegaly or generalized lymphadenopathy attributable to JIA; (3) No active uveitis (as examined by an ophthalmologist); (4) Normal ESR or CRP (if both are tested, both must be normal); (5) Physician global assessment of disease activity indicates no disease activity (i.e. best score on the scale used) (5). A SoJIA relapse was defined as a change in disease status

from inactive to active; the major reasons included infection, inappropriate drug tapering, cease of drug use and excessive exertion.

Statistical analysis

Continuous variables are presented as medians and inter-quartile ranges (IQR, the range between the 25th and 75th percentile) due to non-normal distribution, which were compared between atopy and non-atopy groups by the Mann–Whitney *U* test. Categorical variables were expressed by counts and percentages, and compared between different groups by the Chi-square test or Fisher's exact test. SAS software package, version 9.2 (SAS Institute Inc., Cary, NC) was used for the statistical analysis. All statistic assessments were evaluated at a two sided α level of 0.05. Thus, interpretation of no significant difference in a variable between groups needed restraint.

Results

This prospective study enrolled 61 SoJIA patients diagnosed by rheumatologists at the Renji Hospital between Jan 2006 and Sep 2010. The 34 boys and 27 girls had a mean current age of 9.6 ± 3.3 years and a mean age at diagnosis of 7.4 ± 3.3 years, respectively. The patients were divided into an atopic group ($n = 27$) and a non-atopic group ($n = 34$). The majority of atopic patients were positive for inhaled allergy (77.8%), food allergy (55.6%), and SPT (77.8%). The atopic group had significantly higher median IgE, median ECP, median ferritin, and the median number of affected joints at baseline than the non-atopic group (all $p \leq 0.016$, Table 1).

At the 3rd month, the atopic group had a significantly higher ESR, PLT and systemic feature score than the non-atopic patients (all $p \leq 0.023$). The atopic patients had a significantly higher frequency of elevated ferritin, and a lower frequency of ACR Pedi 50 than non-atopic patients (both $p \leq 0.021$) (Table 2). At the 6th month, the atopic group had significantly higher median ESR and systemic feature score than the non-atopic group (both $p \leq 0.021$). The atopic

patients had a higher frequency of elevated ferritin, and a lower rate of ACR Pedi 30, ACR Pedi 50, and ACR Pedi 70 improvements than non-atopic patients (all $p \leq 0.034$) (Table 2).

Although the course of SoJIA can be classified based on clinical manifestations, such as the number of relapse and remission, the number of patients classified as polycyclic in this study was very small. We therefore grouped patients as monophasic or non-monophasic (which included polycyclic and persistent) and reanalyzed the data (Supplementary Table 1). We showed that IgE levels were significantly elevated in atopic patients in the monophasic as well as non-monophasic groups compared to non-atopic patients ($p < 0.001$). Systemic feature scores and the number of joints affected were significantly higher in atopic patients in the monophasic group compared to non-atopic patients ($p = 0.031$ and 0.008 , respectively). ECP values were also significantly higher in atopic patients in non-monophasic group compared to the non-atopic patients ($p = 0.015$). There was also a significant elevation in ferritin levels among all subjects in the atopic group compared to the non-atopic group ($p = 0.016$) (Supplementary Table 1).

To determine whether the presence of atopy was associated with an altered SoJIA progression profile, we examined the JIA classification of the atopic and non-atopic groups after 2 years. The mean follow-up duration was 27.1 ± 17.4 months among all SoJIA patients. The two groups had used similar types of DMARDs (Methotrexate, Cyclosporine and Leflunomide). Forty four (72.1%) SoJIA patients were traced. Most of the 27 patients in atopic group were classified as non-monophasic (74.1%). In contrast, half of the 34 patients in the non-atopic group were classified as monophasic and the other half as non-monophasic, although the difference between groups did not reach statistical significance. The number of JIA flares of the atopic group was significantly higher than that of the non-atopic group ($p = 0.016$) (Table 3), suggesting that SoJIA patients with atopy have a higher risk for a worse outcome.

Table 1. Demographics and characteristics of SoJIA at baseline.

Characteristic	Non-atopy ($n = 34$)	Atopy ($n = 27$)	<i>p</i> Value
Current age ^a , years	10.5 (7.8, 12.5)	9.2 (6.2, 12.0)	0.266
Gender ^b (Boys)	22 (64.7)	12 (44.4)	0.186
Age at diagnosis ^a , years	7.4 (5.5, 9.9)	6.4 (4.0, 10.0)	0.424
Individual history of inhaled allergy ^b	0 (0.0)	21 (77.8)	<0.001*
Individual history of food allergy ^b	0 (0.0)	15 (55.6)	<0.001*
SPT ^b , positive	0 (0.0)	21 (77.8)	<0.001*
Family history of atopy ^b	6 (17.6)	18 (66.7)	<0.001*
Laboratory features ^a			
IgE, IU/ml	69.3 (25.1, 294.0)	766.0 (248.0, 1045.0)	<0.001*
ECP, $\mu\text{g/L}$	7.5 (4.7, 16.1)	23.8 (10.9, 35.8)	0.006*
CRP, mg/L	89.2 (44.6, 123.0)	91.0 (52.9, 133.0)	0.700
ESR, mm/h	75.0 (44.0, 96.0)	71.0 (55.0, 99.0)	0.481
Ferritin, ng/ml	1232.0 (199.0, 1500.0)	1500.0 (1500.0, 1500.0)	0.016*
Systemic feature score	4.0 (3.0, 5.0)	5.0 (3.0, 7.0)	0.072
Joints affected	2.0 (1.0, 4.0)	5.0 (3.0, 6.0)	<0.001*

CRP, C-reactive protein; ECP, eosinophil cationic protein; ESR, erythrocyte sedimentation rate; IgE, immunoglobulin E; SPT, skin prick test.

^aContinuous data were presented as median (IQR), and compared between different groups by Mann–Whitney *U* test.

^bCategorical variables were expressed by counts and percentages, and compared between different groups by the Chi-square test.

* $p < 0.05$ indicated a significant difference between the different groups.

Table 2. Laboratory features of SoJIA patients at baseline, 3rd and 6th month.

	Non-atopy (<i>n</i> = 34)	Atopy (<i>n</i> = 27)	<i>p</i> Value
ESR, mm/h ^a			
Baseline	75.0 (44.0, 96.0)	71.0 (55.0, 99.0)	0.481
3rd month	13.5 (11.0, 36.0)	32.0 (17.0, 48.0)	0.011*
6th month	14.5 (7.0, 20.0)	25.0 (10.0, 36.0)	0.021*
PLT, × 10 ⁹ /L ^a			
Baseline	Normal range (100–300)	Normal range (100–300)	
3rd month	302.0 (238.0, 364.0)	369.0 (320.0, 412.0)	0.023*
6th month	347.5 (247.0, 425.0)	391.0 (269.0, 456.0)	0.060
Ferritin, ng/ml			
Baseline ^a	1232.0 (199.0, 1500.0)	1500.0 (1500.0, 1500.0)	0.016*
3rd month ^{bc}	14 (41.2)	20 (74.1)	0.021*
6th month ^{bc}	11 (32.4)	17 (63.0)	0.034*
Systemic feature score ^a			
Baseline	4.0 (3.0, 5.0)	5.0 (3.0, 7.0)	0.072
3rd month	1.0 (0.0, 3.0)	3.0 (2.0, 4.0)	0.004*
6th month	0.0 (0.0, 2.0)	3.0 (1.0, 4.0)	<0.001*
Joints affected			
Baseline ^a	2.0 (1.0, 4.0)	5.0 (3.0, 6.0)	<0.001*
3rd month ^{bc}	16 (47.1)	20 (74.1)	0.062
6th month ^{bc}	12 (35.3)	16 (59.3)	0.108
ACR Pedi 30 ^{cd}			
3rd month	23 (67.6)	11 (40.7)	0.065
6th month	29 (85.3)	15 (55.6)	0.022*
ACR Pedi 50 ^{cd}			
3rd month	13 (38.2)	2 (7.4)	0.013*
6th month	22 (64.7)	7 (25.9)	0.006*
ACR Pedi 70 ^{cd}			
3rd month	9 (26.5)	2 (7.4)	0.092
6th month	19 (55.9)	4 (14.8)	0.003*

ESR: erythrocyte sedimentation rate; PLT: platelet count.

^aContinuous data were presented as median (IQR), and compared between different groups by Mann–Whitney *U* test.

^bFollow up measurements at 3rd and 6th month represented numbers of patients with rising values compared to baseline values.

^cCategorical variables were expressed by counts and percentages, and compared between different groups by the Chi-square test.

^dACR Pedi 30, ACR Pedi 50, ACR Pedi 70 was expressed as the number of patients who met ACR Pedi 30, ACR Pedi 50, ACR Pedi 70 definitions at 3rd and 6th month.

**p* < 0.05 indicated a significant difference between the different groups.

Table 3. Clinical features of SoJIA patients at the end of follow-up.

	Non-atopy (<i>n</i> = 34)	Atopy (<i>n</i> = 27)	<i>p</i> Value
Monophasic ^a			0.099
Non-monophasic	17 (50.0)	20 (74.1)	
Monophasic	17 (50.0)	7 (25.9)	
Number of DMARDs taken ^a			0.181
0	10 (29.4)	3 (11.1)	
1	18 (52.9)	16 (59.3)	
2	6 (17.6)	8 (29.6)	
Number of Flares ^b			0.016*
0	15 (44.1)	6 (22.2)	
1	7 (20.6)	2 (7.4)	
2	11 (32.4)	12 (44.4)	
3	1 (2.9)	7 (25.9)	

DMARDs: disease-modifying antirheumatic drugs.

^aCategorical variables were expressed by counts and percentages, and compared between different groups by the Chi-square test or Fisher's exact test.

^bContinuous data were presented as median (IQR), and compared between different groups by Mann–Whitney *U* test.

**p* < 0.05 indicated a significant difference between the different groups.

Discussion

This prospective study of 61 SoJIA patients showed that atopy and SoJIA are not mutually exclusive and atopy may be associated with worse SoJIA symptoms and with significantly greater difficulty in successful management of SoJIA. For example, SoJIA patients with co-existing atopy at diagnosis had significantly more affected joints and significantly higher ferritin levels and IgE serum levels than SoJIA patients without atopy. Improvement of SoJIA symptoms as measured by the ACR Pedi 30, 50, and 70 scores occurred in significantly fewer patients with atopy than those without atopy. However, the finding that patients with SoJIA and atopy experienced significantly more affected joints and a significantly worse prognosis is analogous to the non-monophasic disease course of most JIA patients with polyarthritis²⁴. The 44% prevalence of atopy in our SoJIA patients was higher than the 14.5% prevalence of allergic rhinitis and the 8.7% prevalence of atopic dermatitis in a recent study of adult patients with juvenile idiopathic arthritis²⁵. Interestingly, we showed that SoJIA patients had normal platelet values. Platelets are considered to be a delayed inflammatory indicator, and this value did not rise

initially, or rise slowly. Additionally, platelets are normally elevated in patients treated with hormones. Persistent inflammation for over 6 months is quite normal in a chronic inflammatory disease such as SoJIA.

Common dysregulated pathways that may contribute to the augmented co-morbidity of atopy and SoJIA include Th17 cells, elevated IL-17 production, and NK cell cytotoxicity. Th17 cells and the cytokines, IL-17A, and IL-23, likely contribute to the persistence of chronic inflammation during autoimmune diseases, as higher numbers of infiltrating Th1 and Th17 cells are present in the synovial milieu of SoJIA patients¹³. Higher IL-17 concentrations in the synovial fluid correlated with number of swollen joints, tender joints, and joints with limited range²¹. Th17 cells, which produce IL-17A, also appear to contribute to an atopic disease state by at least three mechanisms: (i) IL-17A promotes B cell immunoglobulin class switching to IgE; (ii) severity of atopic dermatitis correlates with the number of infiltrating and circulating Th17 cells; and (iii) IL-17A reduces filaggrin mRNA expression, which helps maintain the epithelial barrier. Higher numbers of Th17 cells were observed in acute atopic dermatitis lesions but not chronic lesions²⁶. Secondly both SoJIA and atopy have been associated with low cytotoxic activity of NK cells^{19,20,27}. If chronic infections are contributing to the continual innate response in atopy and/or JIA, then the reduced NK cytotoxicity may prolong the resolution of chronic infection.

Patients with atopic dermatitis (AD) have been shown to harbor highly activated NK cells *in vivo*, as indicated by a high spontaneous release of IL-4, IL-5, IL-13, and IFN- γ from isolated lesional NK cells. Analogous to the enhanced polarization toward TH2 cells and their cytokines in early AD lesions, the percentages of IL-5- and IL-13-producing NK cells were significantly higher in patients with AD than in healthy subjects²⁶. It will be interesting to investigate the percentage of activated NK cells in SoJIA patients with concomitant atopy.

Circulating levels of ferritin are thought to play a role in inflammation and to contribute to the pathogenesis of macrophage activation syndrome (MAS), adult onset Still's disease (AOSD), catastrophic antiphospholipid syndrome (cAPS), and septic shock²⁸. Furthermore, the high ferritin levels found in SoJIA may be associated with a future propensity for macrophage activation syndrome (MAS)²⁹, which is characterized by fever, hepatosplenomegaly, lymphadenopathy, severe cytopenia, serious liver disease, intravascular coagulation and/or neurological involvement. However, we believe that we are the first to show elevation in ferritin levels in SoJIA patients with concomitant atopy.

The limitations of this prospective study relate to the relatively small group sizes which would reduce the ability to detect significant differences in variables between the SoJIA patients with atopy and SoJIA patients without atopy. However, SoJIA is a relatively rare disease so we expected slow recruitment. Despite the small group sizes, we are confident of the significantly different variables (number of active joints, ferritin level, improvement with ACR 30/50/70% scales). A larger study may reveal that variables with modest differences in this study may show significant differences.

Our results do not support the hypothesis that allergic syndromes reduce the incidence of SoJIA. In fact, atopy appeared to augment the JIA symptoms and suggests that timely diagnosis and treatment would benefit the patients. The Th1/Th2 paradigm does not explain the relationship between atopy and SoJIA.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

References

1. Ringold S, Beukelman T, Nigrovic PA, Kimura Y. Race, ethnicity, and disease outcomes in juvenile idiopathic arthritis: a cross-sectional analysis of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry. *J Rheumatol* 2013;40:936–942.
2. Beukelman T, Patkar NM, Saag KG, et al. American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. *Arthritis Care Res* 2011;63:465–482.
3. Ramanan AV, Grom AA. Does systemic-onset juvenile idiopathic arthritis belong under juvenile idiopathic arthritis? *Rheumatology* 2005;44:1350–1353.
4. Harris JG, Kessler EA, Verbsky JW. Update on the treatment of juvenile idiopathic arthritis. *Curr Allergy Asthma Rep* 2013;13:337–346.
5. Spiegel LR, Schneider R, Lang BA, et al. Early predictors of poor functional outcome in systemic-onset juvenile rheumatoid arthritis: a multicenter cohort study. *Arthritis Rheum* 2000;43:2402–2409.
6. Frosch M, Roth J. New insights in systemic juvenile idiopathic arthritis – from pathophysiology to treatment. *Rheumatology* 2008;47:121–125.
7. Russo RA, Katsicas MM. Patients with very early-onset systemic juvenile idiopathic arthritis exhibit more inflammatory features and a worse outcome. *J Rheumatol* 2013;40:329–334.
8. Vastert SJ, Kuis W, Grom AA. Systemic JIA: new developments in the understanding of the pathophysiology and therapy. *Best Pract Res Clin Rheumatol* 2009;23:655–664.
9. Rossi-Semerano L, Kone-Paut I. Is Still's disease an autoinflammatory syndrome? *J Inflamm* 2012;2012:480373.
10. Ronchetti R, Rennerova Z, Barreto M, Villa MP. The prevalence of atopy in asthmatic children correlates strictly with the prevalence of atopy among nonasthmatic children. *Int Arch Allergy Immunol* 2007;142:79–85.
11. Shah A. The pathologic and clinical intersection of atopic and autoimmune disease. *Curr Allergy Asthma Rep* 2012;12:520–529.
12. Omoyinmi E, Hamaoui R, Pesenacker A, et al. Th1 and Th17 cell subpopulations are enriched in the peripheral blood of patients with systemic juvenile idiopathic arthritis. *Rheumatology* 2012;51:1881–1886.
13. Lin YT, Wang CT, Gershwin ME, Chiang BL. The pathogenesis of oligoarticular/polyarticular vs systemic juvenile idiopathic arthritis. *Autoimmun Rev* 2011;10:482–489.
14. Macaubas C, Nguyen K, Deshpande C, et al. Distribution of circulating cells in systemic juvenile idiopathic arthritis across disease activity states. *Clin Immunol* 2010;134:206–216.
15. Abbas AK, Murphy KM, Sher A. Functional diversity of helper T lymphocytes. *Nature* 1996;383:787–793.
16. Sheikh A, Smeeth L, Hubbard R. There is no evidence of an inverse relationship between TH2-mediated atopy and TH1-mediated autoimmune disorders: lack of support for the hygiene hypothesis. *J Allergy Clin Immunol* 2003;111:131–135.
17. Gazit V, Tasher D, Hanukoglu A, et al. Atopy in children and adolescents with insulin-dependent diabetes mellitus. *Isr Med Assoc J* 2008;10:858–861.
18. Lindelof B, Granath F, Tengvall-Linder M, et al. Allergy and autoimmune disease: a registry-based study. *Clin Exp Allergy* 2009;39:110–115.

19. Koh YI, Shim JU, Wi JO, et al. Inverse association of peripheral blood CD4(+) invariant natural killer T cells with atopy in human asthma. *Hum Immunol* 2010;71:186–191.
20. Villanueva J, Lee S, Giannini EH, et al. Natural killer cell dysfunction is a distinguishing feature of systemic onset juvenile rheumatoid arthritis and macrophage activation syndrome. *Arthritis Res Ther* 2005;7:R30–R37.
21. Agarwal S, Misra R, Aggarwal A. Interleukin 17 levels are increased in juvenile idiopathic arthritis synovial fluid and induce synovial fibroblasts to produce proinflammatory cytokines and matrix metalloproteinases. *J Rheumatol* 2008;35:515–519.
22. Davidson J, Cruikshank M. Outcome for juvenile idiopathic arthritis. *Paediatr Child Health* 2009;20:73–78.
23. Yokota S, Imagawa T, Mori M, et al. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. *Lancet* 2008;371:998–1006.
24. Singh-Grewal D, Schneider R, Bayer N, Feldman BM. Predictors of disease course and remission in systemic juvenile idiopathic arthritis: significance of early clinical and laboratory features. *Arthritis Rheum* 2006;54:1595–1601.
25. Raab A, Sengler C, Niewerth M, et al. Comorbidity profiles among adult patients with juvenile idiopathic arthritis: results of a biologic register. *Clin Exp Rheumatol* 2013;31:796–802.
26. von Bubnoff D, Andres E, Hentges F, et al. Natural killer cells in atopic and autoimmune diseases of the skin. *J Allergy Clin Immunol* 2010;125:60–68.
27. Zhou J, Tang X, Ding Y, et al. Natural killer cell activity and frequency of killer cell immunoglobulin-like receptors in children with different forms of juvenile idiopathic arthritis. *Pediatr Allergy Immunol* 2013;24:691–696.
28. Rosario C, Zandman-Goddard G, Meyron-Holtz EG, et al. The Hyperferritinemic Syndrome: macrophage activation syndrome, Still's disease, septic shock and catastrophic antiphospholipid syndrome. *BMC Med* 2013;11:185.
29. Fall N, Barnes M, Thornton S, et al. Gene expression profiling of peripheral blood from patients with untreated new-onset systemic juvenile idiopathic arthritis reveals molecular heterogeneity that may predict macrophage activation syndrome. *Arthritis Rheum* 2007;56:3793–3804.

Supplementary material available online.

Supplementary Table 1.

Supplementary Table 1. Clinical features of monophasic and non-monophasic SoJIA patients at baseline

	All subject			Monophasic			Non-monophasic		
	non-atopic (n=34)	Atopic (n=27)	P-value	non-atopic (n=17)	Atopic (n=7)	P-value	non-atopic (n=17)	Atopic (n=20)	P-value
IgE, IU/ml	69.3 (25.1, 294.0)	766.0 (248.0, 1045.0)	<0.001	143.0 (25.1, 294.0)	827.0 (245.0, 2000.0)	0.016	67.2 (34.4, 108.0)	629.0 (274.0, 1020.5)	<0.001
ECP, µg/L	7.5 (4.7, 16.1)	23.8 (10.9, 35.8)	0.006	9.5 (7.2, 19.0)	24.3 (10.5, 38.9)	0.162	6.2 (4.6, 13.8)	21.2 (11.3, 34.1)	0.015
CRP, mg/L	89.2 (44.6, 123.0)	91.0 (52.9, 133.0)	0.700	78.7 (36.9, 113.0)	116.0 (93.4, 133.0)	0.092	102.0 (55.8, 126.0)	65.5 (44.3, 128.5)	0.493
ESR, mm/h	75.0 (44.0, 96.0)	71.0 (55.0, 99.0)	0.481	76.0 (40.0, 101.0)	69.0 (65.0, 120.0)	0.525	75.0 (62.0, 91.0)	73.5 (55.0, 94.5)	0.692
Ferritin, ng/ml	1232.0 (199.0, 1500.0)	1500.0 (1500.0, 1500.0)	0.016	1040.0 (199.0, 1500.0)	1500.0 (1500.0, 1500.0)	0.096	1500.0 (890.0, 1500.0)	1500.0 (1500.0, 1500.0)	0.152
Systemic feature score	4.0 (3.0, 5.0)	5.0 (3.0, 7.0)	0.072	4.0 (3.0, 5.0)	6.0 (4.0, 8.0)	0.031	4.0 (3.0, 8.0)	5.0 (3.0, 6.5)	0.889
Joints affected	2.0 (1.0, 4.0)	5.0 (3.0, 6.0)	<0.001	2.0 (1.0, 2.0)	6.0 (4.0, 6.0)	0.008	3.0 (2.0, 4.0)	4.0 (3.0, 6.0)	0.054

IgE, Immunoglobulin E; ECP, eosinophil cationic protein; CRP , C-Reactive Protein; ESR, Erythrocyte sedimentation rate.

Continuous data were presented as median (IQR), and compared between different groups by Mann-Whitney U test.

*p<0.05 indicated a significant difference between the different groups.