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Interleukin-18 as a mediator of systemic juvenile idiopathic arthritis

Brief report

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Running title: Interleukin-18 in juvenile idiopathic arthritis

Abstract

The objective of this report is to explore the balance between serum and synovial fluid levels of interleukin (IL)-18 in children with juvenile idiopathic arthritis (JIA).

Blood samples were obtained from 81 children with JIA and 18 control children. Synovial fluid samples were collected from 16 children with oligoarticular JIA. Concentrations of IL-18 were determined using commercial kit.

Patients with systemic JIA had higher serum levels of IL-18 than patients with other forms of JIA or control children, both during the active (median, range: 6240, 1600 – 78750 pg/mL) and inactive (1615, 513 – 3270 pg/mL) phase of disease (ANOVA, $P<0.05$). Levels of IL-18 in sera of children with oligoarticular JIA (255, 89 – 4342 pg/mL) were similar to the respective synovial fluid levels (217, 89 – 1245 pg/mL). Serum levels of IL-18 were proportional to the erythrocyte sedimentation rate and levels of C-reactive protein, but inversely proportional to the haemoglobin levels.

IL-18 appears to be an important mediator of systemic JIA, while it seems of a lesser relevance in pathogenesis of other JIA forms. Therefore, inhibition of IL-18 might be a base for a successful biologic therapy of systemic JIA.

Key words: Inflammation, interleukin-18, juvenile idiopathic arthritis

Introduction

Juvenile idiopathic arthritis (JIA) comprises a heterogeneous group of clinical conditions with unknown aetiology. Pathogenesis of JIA is not fully understood but it seems that, in genetically susceptible individuals, various triggering factors (e.g. trauma, joint infection, hormone levels) may lead to the immune dysbalance and subsequent articular and systemic manifestations [1].

Several aspects of immune dysregulation in JIA have been described, including alteration of regulatory T cell numbers, as well as abnormal chemokine and cytokine production, especially IL-1β, IL-6 and TNF-α [2-5]. Among the cytokines, IL-18 should also be particularly interesting with respect to the pathogenesis of JIA. IL-18 stimulates a variety of inflammatory responses, enhances proliferation and activity of T cells and NK cells, and shifts helper T cell balance towards Th1 response [6,7]. We suspected that IL-18 is not only a prominent mediator of JIA, but that different forms of JIA could be associated with different levels of IL-18 as well. Therefore, to get an insight into role of IL-18 in JIA, we aimed to explore the serum levels of IL-18 both during the active and quiescent phases of the disease.

Materials and methods

A total of 81 children (50 girls, 31 boys; median age 7, range 1 – 19 years), consecutively admitted at the Division of Paediatric Rheumatology between December 2002 and April 2005 with the diagnosis of JIA, were included in the present study. Out of those 81 children, 31 had oligoarticular JIA, 33 had polyarticular JIA, and 17 had the systemic form of JIA, in accordance to the ILAR criteria [8]. In addition, we included a control group of 18 randomly selected children (9 girls, 9 boys; median age 10.5, range 2 – 16 years), who were admitted at the Division due to non-inflammatory conditions, during the same period. The study was approved by the Ethics Committee of the Zagreb University School of Medicine.

Peripheral blood was obtained from each patient in both active phase of disease and, later, in clinical remission, which we, according to Walace and her co-workers, referred to as "inactive on medication" [9]. The criteria for inactive phase on medication were following: no active arthritis, fever, rash, hepatosplenomegaly, generalized lymphadenopathy, active uveitis, and serositis; normal erythrocyte sedimentation rate and C-reactive protein levels; during a minimum of six continuous months while receiving medication. In addition, synovial fluid samples were collected at the same time as the peripheral blood from 16 patients with the oligoarticular form of JIA. Routine laboratory tests were performed at the Department of Clinical Laboratory Diagnostics. Serum and synovial fluid concentrations of IL-18 were determined using commercially available kit, following the manufacturers' recommendations (Human IL-18 ELISA Kit, Medical & Biological Laboratories Co., Naka-ku Nagoya, Japan).

Data were summarised using median and range. The groups were compared by ANOVA, followed by Student-Newman-Keuls *post hoc* test, while the bivariate relationships were analysed using Spearman's ρ. Comparisons within the group (i.e. active phase vs. inactive on medication) were performed using Student's t-test for dependent samples. The α-level was set at 0.05. MedCalc for Windows (MedCalc Software, Mariakerke, Belgium) was used for the analyses.

Results

During the active phase of JIA, children with systemic form of disease had higher serum levels of IL-18 than children with oligoarticular or polyarticular form (ANOVA and Student-Newman-Keuls *post hoc* test, $F_{3,95} = 9.282$, $P < 0.001$) (Table I). The same pattern was observed in the inactive phase: children with systemic JIA had the highest serum levels of IL-18 (ANOVA and Student-Newman-Keuls *post hoc* test, $F_{3,91} = 54.651$, $P < 0.001$). Serum levels of IL-18 in children with systemic JIA during the remission were significantly lower compared to the levels found in the active phase (Student's t-test for dependent samples, $t_{15} = -5.197$, $P < 0.001$). On the other hand, synovial concentrations of IL-18 in 16 patients with oligoarticular JIA (median, range: 206, 23 – 832 pg/mL; n = 16) did not differ significantly from serum levels of IL-18 in the same patients (median, range: 217, 89 – 1245 pg/mL) (Student's t-test, $P = 0.555$).

The serum levels of IL-18 in the active phase of all patients correlated well with several laboratory tests, commonly used to evaluate a status of JIA patient: erythrocyte sedimentation rate ($\rho = 0.33$, $P = 0.001$), C-reactive protein level ($\rho = 0.39$, $P < 0.001$), haemoglobin level ($\rho = -0.35$, $P < 0.001$), haematocrit ($\rho = -0.37$, $P < 0.001$), platelet count ($\rho = 0.28$, $P = 0.014$), and α2-globulin levels ($\rho = 0.35$, $P = 0.002$). Some associations were found to be significant even during the remission, although they were weaker when compared to the active phase: haemoglobin level ($\rho = -0.22$, $P = 0.038$), haematocrit ($\rho = -0.25$, $P = 0.020$), and platelet count ($\rho = 0.25$, $P = 0.033$).

Discussion

Results of the present study point to the increased levels of IL-18 in the systemic form of JIA. Although the elevation of IL-18 levels has been reported in children with systemic JIA and patients with adult-onset Still's disease [10,11], we have clearly shown that the serum levels of IL-18 in systemic JIA remain high even during the inactive phase on medication. In addition, the serum concentrations of IL-18 correlated well with several laboratory indicators of inflammation, both during active and, although to the lesser extent, inactive on medication phase of JIA. Taken together, the findings indicate that IL-18 could contribute to the pathogenesis of the inflammatory process in systemic JIA, not only during the exacerbation, but also during the clinically silent phase of the disease. On the other hand, it could be inferred that IL-18 is not a major mediator of oligoarticular or polyarticular JIA.

Furthermore, our study was, to the best of our knowledge, the first to determine the articular concentrations of IL-18 in active phase of JIA, at the beginning, or at the early stage of disease. As IL-18 is involved in the pathogenesis of articular damage in rheumatoid arthritis [12] and the elevated expression of IL-18 mRNA was described in affected joints of JIA patients [13], we expected to find abundant levels of IL-18 in the synovial fluid of the inflamed joints. Surprisingly, the serum levels of IL-18 in children with oligoarticular JIA were comparable to the synovial levels of the same cytokine, indicating that the pathogenesis of arthritis in oligoarticular JIA is probably mediated by other tissue factors, but not IL-18.

We also have to note certain limitations of our work. First, number of patients with systemic JIA was relatively small. Furthermore, we focused on only one cytokine, while it is know that interactions between cytokine and chemokines are very complex and to fully understand the role of IL-18 in pathogenesis of JIA, relationship between IL-18 and other mediators should be explored.

In spite of limitations, the data presented in the manuscript indicate that IL-18 could be involved in the systemic inflammation within the course of JIA. Increased levels of IL-18 during the remission on medication of systemic JIA might imply that the inflammatory process is still active, although the patients' erythrocyte sedimentation rates and C-reactive protein levels were within the limits of the normal findings. Thus, monitoring of IL-18 levels could prove out to be a useful prognostic tool. Furthermore, our results suggest that IL-18 could be an excellent target for biologic therapy of systemic JIA.

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Table I. Serum concentrations of interleukin-18 (median, range) (pg/mL) in 81 children with juvenile idiopathic arthritis (JIA) and 18 control children, during the active phase and in inactive phase on medication.

group	n	active phase	inactive on medication
oligoarticular JIA	31	255 (89 – 4342)	201 (76 – 842)
polyarticular JIA	33	271 (126 – 3690)	208 (83 – 996)
systemic JIA	17	6240 (1600 – 78750)*	1615 (513 – 3270)*†
control	18	315 (176 – 439)	

* P<0.001 vs. the other groups during the same phase, ANOVA and Student-Newman-Keuls test

† P<0.001 vs. active phase, Student's t-test for dependent samples