

IMMUNOGLOBULIN E-RHEUMATOID FACTOR IN JUVENILE RHEUMATOID ARTHRITIS

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OBJECTIVES: To determine the presence of immunoglobulin E-rheumatoid factor in patients with juvenile rheumatoid arthritis and to correlate it with clinical and laboratory parameters.

METHODS: A multicenter prospective study was carried out from January 1993 to January 1999 with the enrollment of 3 centers of pediatric rheumatology. Ninety-one children with juvenile rheumatoid arthritis diagnosed according to the American College of Rheumatology criteria were studied: 38 (42%) with systemic, 28 (31%) with pauciarticular, and 25 (27%) with polyarticular onset. Ages ranged from 2.1 years to 22.6 years (mean 10.5 ± 4.7), with 59 (65%) girls. The control group consisted of 45 healthy children. The detection of immunoglobulin E-rheumatoid factor was carried out utilizing an enzyme-linked immunosorbent assay. Associations of immunoglobulin E-rheumatoid factor with immunoglobulin M-rheumatoid factor (latex agglutination test), total serum immunoglobulin E, erythrocyte sedimentation rate, antinuclear antibody, and functional and radiological classes III or IV were analyzed.

RESULTS: Positive immunoglobulin E-rheumatoid factor was found in 15 (16.5%) of the 91 children with juvenile rheumatoid arthritis: 7 (18.5%) with systemic, 5 (18%) with pauciarticular, and 3 (12%) with polyarticular onset. A significant correlation was observed between immunoglobulin E-rheumatoid factor and total serum immunoglobulin E in the juvenile rheumatoid arthritis patients. No correlation was found between immunoglobulin E-rheumatoid factor and positive latex agglutination slide test, erythrocyte sedimentation rate, antinuclear antibody, or the functional and radiological classes III or IV in any disease onset group. In 4 out of 45 control children (8.9%), immunoglobulin E-rheumatoid factor was positive but with no correlation with total serum immunoglobulin E levels.

CONCLUSIONS: Immunoglobulin E-rheumatoid factor could be detected in 16.5% of juvenile rheumatoid arthritis patients, particularly in those with high levels of total serum immunoglobulin E, and immunoglobulin E-rheumatoid factor appears not to be associated with disease activity or severity.

DESCRIPTORS: Rheumatoid factor. Immunoglobulin E. Juvenile rheumatoid arthritis. ELISA.

INTRODUCTION

Rheumatoid factors (RF) are specific autoantibodies directed against antigenic determinants on the Fc fragment of the IgG molecule¹. However, RFs are not unique to rheumatoid arthritis; they sometimes occur in normal elderly individuals, healthy immunized individuals, and patients with other autoimmune diseases or chronic

infections². Several studies have shown that only 5% to 25% of children with juvenile rheumatoid arthritis (JRA) have positive latex agglutination tests for RF³.

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RFs of the IgM immunoglobulin class can be detected by employing the commonly used agglutination test. These antibodies directed to IgG are the "classic" RFs that are associated with adult-onset rheumatoid arthritis. They are found in only a small subgroup of children who have RF-positive polyarthritis, the disease that is probably the childhood equivalent of classic adult rheumatoid arthritis⁴.

Children with JRA who are RF positive are likely to be girls, to be older at disease onset, and to have many joints involved. It has been suggested that they have more roentgenographic evidence of bony erosion and an overall poorer prognosis than their rheumatoid factor-negative counterparts⁵. Some clinical and immunogenetic associations are well known, such as nodes, bony erosions, functional incapacities, and HLA Dw4 (DRB1*0401) and Dw14 (BRB1*0404) associations^{5,6}.

In one-third of patients with JRA who present idiopathic expression with cross-reaction for RF, classical RF (IgM-RF) is not observed⁷. It is possible that in this group of patients, other RF isotypes are present⁸. With the use of ELISA, an increased detection is observed in JRA, with IgM-RF being demonstrated in 22% to 35% of patients, IgG-RF in 4% to 6%, and IgA-RF in 30% to 60%, depending on the type of disease onset⁹⁻¹¹. The presence of IgA-RF and IgM-RF has been observed in a varying percentage of children with JRA, mainly in the polyarticular onset type^{12,13}. However, the frequency and clinical and prognostic roles of the other RF isotypes (IgG and IgE) in JRA are still unknown¹⁴.

There is evidence suggesting that IgE-RF is associated with extra-articular rheumatoid vasculitis and activity of the disease in rheumatoid arthritis^{15,16}. We found 1 study about IgE-RF in JRA in the literature¹⁷. These investigators observed that sera from 11/26 children with JRA had low concentrations of IgE-RF detected by the indirect immunofluorescence technique and suggested that IgE-RF may be involved in the pathogenesis of JRA and rheumatoid arthritis by eliciting type I and III reactions¹⁷.

The aims of the present study were to determine the presence and the levels of IgE rheumatoid factor (IgE-RF) in children with JRA and to correlate its presence with sex, age at onset, dis-

ease duration, activity of disease, erythrocyte sedimentation rate, antinuclear antibody, total serum IgE, IgM-RF (latex agglutination), and functional and radiological classes III or IV.

PATIENTS AND METHODS

Patients

A prospective, multicentric study was carried out from January 1993 to January 1999. Ninety-one children (59 girls) with JRA diagnosed according to the American College of Rheumatology criteria^{18,6} were studied. Sera were randomly obtained from patients who visited one of the following three Centers of Pediatric Rheumatology: Hospital de Clínicas da Universidade de São Paulo, São Paulo (51 cases), Hospital de Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo, Ribeirão Preto, São Paulo (28 cases), and Hospital de Clínicas da Universidade Federal de Uberlândia, Minas Gerais (12 cases). The age of the patients ranged from 2.1 to 22.7 years (mean 10.5 ± 4.7). The type of disease onset was systemic in 38 children, pauciarticular in 28, and polyarticular in 25.

Forty-five healthy control children with no symptoms of connective tissue disease or acute or chronic infections were selected from the pediatric outpatient clinic. The mean age of controls was 5.5 ± 3.3 years.

Inclusion criteria

All patients included had no clinical symptoms suggestive of allergic rhinitis, asthma, or atopic dermatitis. In addition, they had 3 samples of feces examined for helminths with negative results. None of the JRA patients were receiving or had received gold salts or D-penicillamine.

METHODS

Serum was obtained from each patient during the first appointment after obtaining fully informed consent from their parents or relatives. Approval for the study was also obtained from the 3 Institutional Ethics Committees. Serum samples were stored at -20°C.

The demographic and clinical characteristics of the JRA patients are shown in table 1 (sex, age at onset, disease duration, and activity of disease). Serum was obtained from each patient for the following laboratory measurements: erythrocyte sedimentation rate (by the Wintrobe method), antinuclear antibody (by the Hep 2 immunoassay method), and total serum IgE (measured by monoclonal antibody-based ELISA modified from a previously described radioimmunoassay (RIA) by Pollart¹⁹). Values of total IgE ≥ 300 IU/mL were considered abnormally high (positive)²⁰. IgM-RF was determined by the latex agglutination slide test using a commercially available kit (RapiTex[®] RF, Hoechst, Marburg, Germany). Samples with RF of 20 IU/mL or more were considered to be positive.

Active disease was defined by the presence of joint swelling or limitation of mobility with warmth, pain, or tenderness in 1 or more joints. Severity was evaluated according to Steinbrocker's functional and radiological classes²¹ with classes III and IV denoting major dysfunction.

Quantitative determination of the IGE rheumatoid factor by ELISA

IgE-RF was determined by a standard ELISA technique according to SILVA²², with some modifications. The samples were always analyzed in duplicate.

Briefly, polystyrene microtiter plates were coated with 10 µg/mL of mouse IgG in 0.06 M carbonate buffer, pH 9.6, overnight at 4°C. Plates were

Table 1 - Clinical and laboratory features of the children with juvenile rheumatoid arthritis (n= 91) according to disease onset (systemic, pauciarticular, or polyarticular).

Clinical and Laboratory Features	JUVENILE RHEUMATOID ARTHRITIS			
	Total (n = 91)	Systemic (n = 38)	Pauciarticular (n = 28)	Polyarticular (n = 25)
Females	59 (64.4%)	21 (55.3%)	17 (60.71%)	21 (84%)
Age (years)	10.5 (2.1 – 22.7)	11 (4.1 – 20.8)	9.9 (2.4-17.2)	10.3 (4.2-18.6)
Disease duration (years)	5.2 (0.2– 17.3)	6.2 (1.1-13.6)	4.4 (0.7-10.2)	3.7 (0.2-11.6)
Age at onset (years)	5.2 (0.5 – 16.1)	4.7 (1.4-11.9)	5.5 (1.1-13.3)	6.7 (2.9-12.2)
Active disease	50 (55%)	21 (55.3%)	12 (42.8%)	17 (68%)
Erythrocyte sedimentation rate (>20 mm/h)	54 (59%)	26 (68.4%)	12 (42.8%)	16 (64%)
Anti nuclear antibody +	19 (21%)	1 (2.6%)	8 (28.6%)	10 (40%)
Rheumatoid factor (latex agglutination +)	5 (5.4%)	—	—	5 (20%)
Functional class (III/IV)	13 (14%)	11 (28.9%)	—	2 (8%)
Radiological class (III/IV)	49 (54%)	26 (68.4%)	10 (35.7%)	13 (52%)
Elevated total serum IgE (>300 IU/mL)	54 (59.3%)	26 (68.4%)	15 (53.6%)	13 (52%)

washed in 0.01M phosphate buffered saline (PBS), pH 7.2, containing 0.05% Tween 20 (PBS-T) and blocked with PBS-T plus 1% bovine serum albumin (PBS-T-BSA) for 1 h at room temperature (RT). Washings in PBS-T were done between the steps of the reaction. The plates were incubated with serum samples diluted 1:5 in PBS-T, in duplicate, for 1 h at RT. Subsequently, peroxidase-rabbit IgG anti-human IgE, prepared as described by Wilson and Nakane²³, at 1:500 in PBS-T was added and incubated for 1 h at RT. Finally, enzymatic substrate consisting of 0.03% H₂O₂ and ortho-phenylenediamine in 0.1 M phosphate citrate buffer, pH 5.0, was added and incubated for 15 min at RT. Adding 2 N H₂SO₄ stopped the reaction, and the absorbancy was read at 492 nm in a plate reader (Titertek Multiskan, Flow Laboratories, USA). Two positive and 10 negative control sera were included in each assay. Positive sera were obtained from patients who had IgM-RF by the latex agglutination test and IgE-RF by previous ELISA tests in the standardization of the assays. Negative sera were obtained from healthy children.

The results were expressed as ELISA index (EI) and calculated as follows: EI = absorbancy of serum

samples / cut off, where cut off was determined as the mean absorbancy of the negative control serum plus 3 standard deviations. Samples presenting EI values > 1 were considered positive.

STATISTICS

Statistical analysis consisted of determinations of geometric means with 95% confidence intervals (CI) for measurements of total serum IgE. Comparisons between the ages of children with JRA were performed using the Student *t* test. This test was also used to compare the geometric means of total serum IgE. The positive and negative samples were listed in contingency tables and analyzed by the χ^2 and Fisher exact tests²⁴. Significance was accepted when *P* <0.05. Statistical calculations were performed using a standard Statistical Package Social Science (SPSS) program.

RESULTS

IgE-RF was detected in 15/91 (16.5%) patients with JRA and 4/45 (8.9%) children from the control group (*P* >0.05) (Fig. 1A). Disease onset was

systemic in 7 (18.4%), pauciarticular in 5 (17.8%), and polyarticular in 3 (12%) (Fig.1B).

An attempt was made to compare IgE-RF-positive and negative patients in the JRA groups. Comparisons of the most significant clinical features between the groups (with or without IgE-RF) are shown in table 2. There was no significant difference between the clinical and laboratory factors (disease activity, erythrocyte sedimentation rate, antinuclear antibody, or functional and radiological class III or IV) and the presence or not of the IgE-RF, except for the log of geometric mean of the total serum IgE, which was significantly higher (*P* = 0.03) in the group of patients with positive IgE-RF (Table 2).

The presence or absence of IgE-RF in sera from JRA patients and control children was analyzed in comparison to total serum IgE (Fig. 2). There was a significant difference (*P* <0.05) in the geometric mean of total IgE between JRA patients with positive (1420 IU/mL) and negative (402 IU/mL) IgE-RF. In contrast, no statistically significant difference was found between positive (157 IU/mL) and negative (117 IU/mL) IgE-RF in the control group (*P* >0.05). In addition, the mean of total IgE values for JRA patients

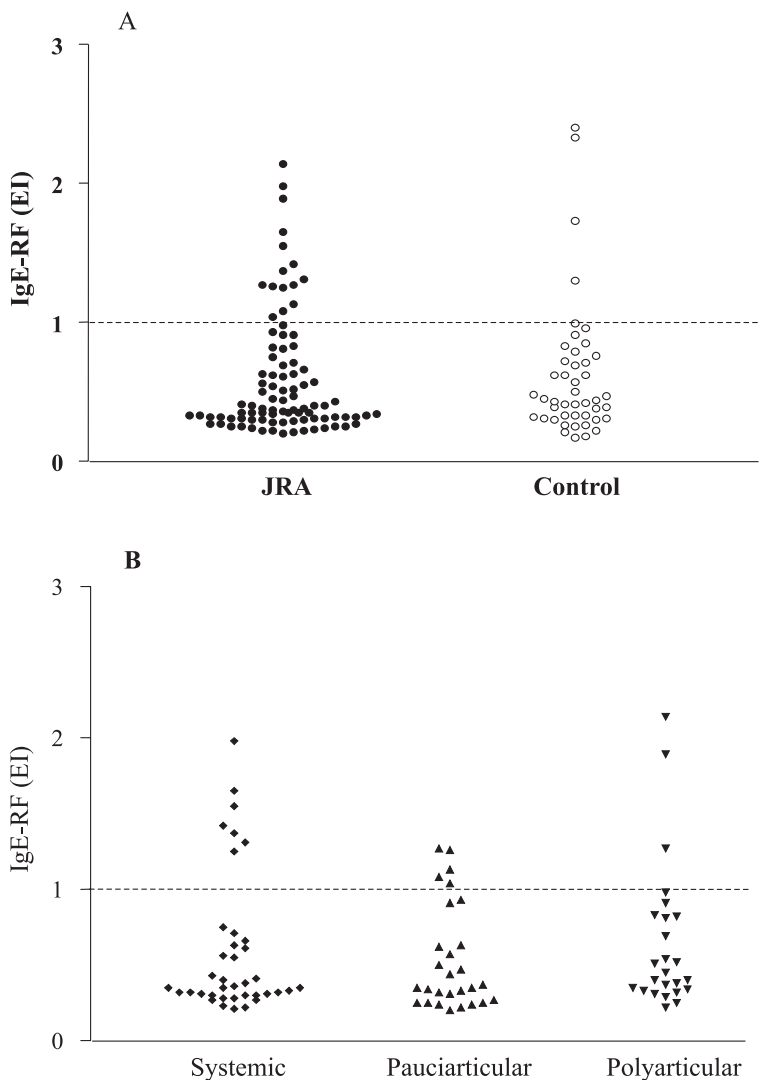


Figure 1 - Levels of IgE-RF expressed in ELISA Index (EI). (A) Patients with JRA (n = 91) and control children (n = 45). (B) JRA patients distributed according to the systemic (n = 38), pauciarticular (n = 28), and polyarticular (n = 25) disease onset. The dashed line represents the cut off of IgE-RF ELISA (EI >1).

with IgE-RF was higher than that obtained for IgE-RF-positive control children, although the difference was not statistically significant ($P = 0.055$).

The geometric mean of total serum IgE for all JRA patients (495 IU/mL) was significantly higher than for the control group (121 IU/mL), $P < 0.0001$ (Fig 3).

DISCUSSION

The pathogenic role of the rheumatoid factor isotypes in JRA is not fully understood¹⁴. The importance of the IgM isotype detected by agglutination methods is clear in terms of the classification and prognosis of this disease, because this isotype defines the seropositive polyarticular subtype, and it is related to progression to erosive disease⁴. However, few studies are available on other RF isotypes in JRA¹⁴. Only 1 investigation assessing the presence of IgE-RF in children with JRA was found in the literature¹⁷. Eleven out of 26 children studied (42%) presented weakly positive reactions (undiluted sera) for IgE-RF when tested by indirect immunofluorescence¹⁷.

In our study, IgE-RF was detected by ELISA in 15 (16.5%) of 91 children with JRA, and this detection was not

Table 2 - Laboratory and clinical features among 15 patients with positive FR-IgE with juvenile rheumatoid arthritis (JRA) and 76 patients with negative IgE-RF.

Laboratory and Clinical Features	Positive IgE-RF n (%)	Negative IgE-RF n (%)	P X ² or Fisher
Active disease	8 (53.3)	42 (55.3)	NS
Erythrocyte sedimentation rate (>20 mm/h)	7 (46.7)	47 (61.8)	NS
Antinuclear antibody (+)	4 (26.7)	15 (19.7)	NS
Rheumatoid factor (latex agglutination +)	2 (13.3)	3 (3.9)	NS
Functional class (III/IV)	2 (13.3)	11 (14.5)	NS
Radiological class (III/IV)	7 (46.7)	42 (55.3)	NS
Log (geometric mean) of the total serum IgE	3.2*	2.2	$P = 0.03$

NS = Not significant.

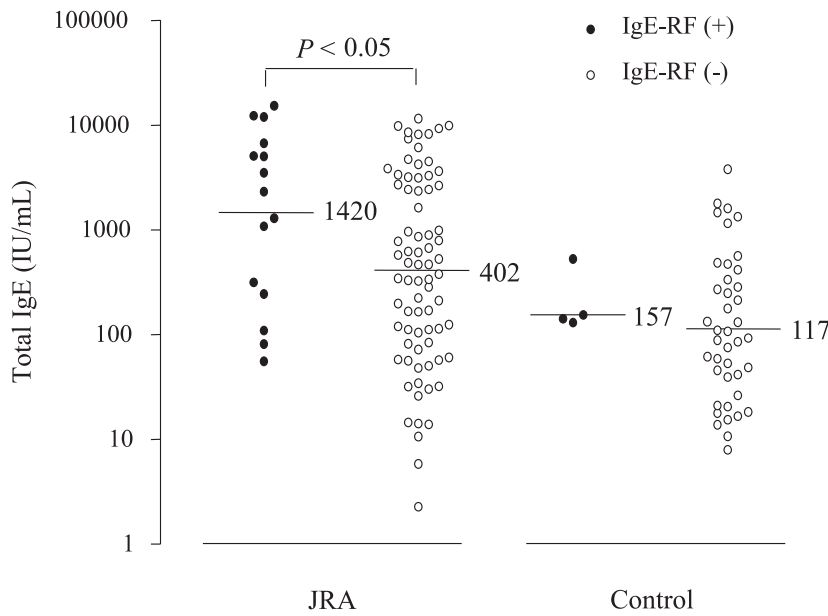


Figure 2 - Levels of total serum IgE in JRA patients with positive IgE-RF (n = 15) and negative IgE-RF (n = 76), and control children with positive IgE-RF (n= 4) and negative IgE-RF (n = 41). The horizontal bars indicate the geometric means.

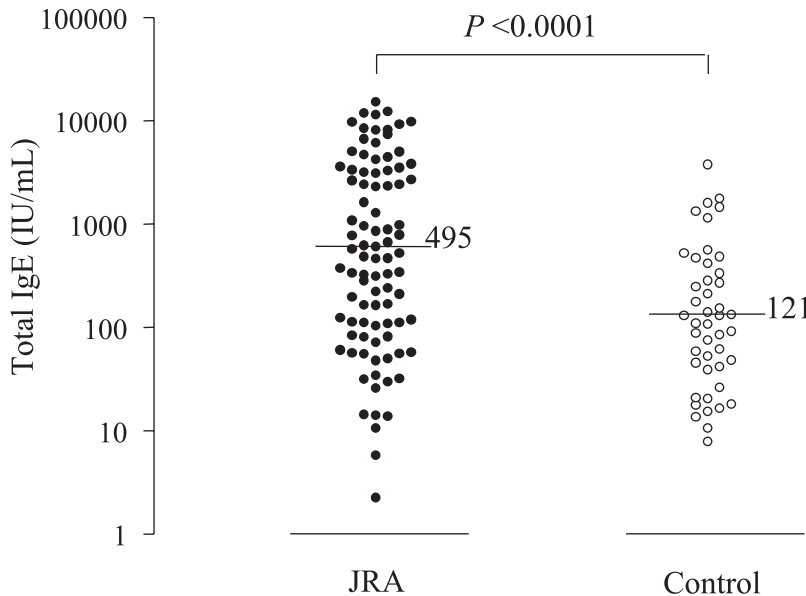


Figure 3 - Levels of total serum IgE expressed in IU/mL in the group of JRA patients (n = 91) and control children (n= 45). The horizontal bars indicate the geometric means.

related to the disease onset type. No correlation was observed between the presence of IgE-RF and any clinical or laboratory parameter. Previous studies have shown that low serum IgE-RF concentrations are detected in approxi-

mately half the patients with rheumatoid arthritis, and high concentrations are detected in patients with vasculitis and other extra-articular manifestations and in patients with Felty's syndrome^{15,16,25}.

In our study, IgE-RF was detected in 4 (8.9%) control children, and at high concentrations in some of them, indicating a low specificity of this antibody. The children in this group were considered healthy, with no clinical history suggestive of atopy. However, it should be emphasized that in the patients with JRA studied here, the presence of IgE-RF was correlated with higher serum IgE concentrations, whereas this was not observed in the IgE-RF positive control group. These data seem to indicate that the stimuli responsible for IgE-RF production is different in healthy individuals and in patients with JRA.

The identification of IgE-RF in a group of patients with JRA stimulates the discussion of the role of this autoantibody and consequently of the IgE-dependent mechanisms involved in the pathogenesis of this disease. The prevalence of atopic disease in children with JRA is unknown. It has been reported that the incidence of IgE-specific antibodies against pollen allergens in 40 children with JRA was similar to that expected for the normal population²⁶. Some studies have suggested that the prevalence of atopy among adults with rheumatoid arthritis is equal to or lower than that observed in the normal population, although high concentrations of total serum IgE have been detected in these patients^{14,26}. Recently, Millauer in 1999, comparing patients with rheumatoid arthritis and patients with allergic diseases, observed that rheumatoid sera have high concentrations of total serum IgE and complexed anti-IgE, in addition to increased reactivity of specific IgE against only 1 allergen (*Alternaria*) and not against 9 other common allergens. Based on these findings, the authors concluded that the presence of large amounts of IgE probably does not result in an increased prevalence of allergic diseases in patients with rheumatoid arthritis, as previously mentioned¹⁴. On the other

hand, the presence of anti-IgE antibodies seems to be paradoxical. According to these authors, it is possible that anti-IgE antibodies may interfere with IgE binding, thus preventing the sensitization of basophils and mast cells³⁴.

Some interesting studies have demonstrated the presence of activated mast cells in experimental rheumatoid lesions²⁷ and in synovial fluid of pa-

tients with rheumatoid arthritis and JRA²⁸, the increased expression of the CD23 antigen in peripheral mononuclear cells of patients with rheumatoid arthritis^{29,30} and JRA³¹, and the reproduction of an experimental model of arthritis by the inoculation of monomeric or complexed IgE^{32,33}. However, the value of these findings for the understanding of the physiopathological mechanisms involved in

rheumatoid synovitis is uncertain.

In conclusion, IgE-RF can be detected in some patients with JRA with higher total serum IgE levels. We believe that the results reported here suggest an alteration of the humoral immune response in some children with JRA and stimulate future research lines aiming at the study of the IgE-dependent biological mechanisms involved in this disease.

RESUMO

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FERREIRA RA e col. - Fator reumatóide-imunoglobulina E na artrite reumatóide juvenil. **Rev. Hosp. Clín. Fac. Med. S. Paulo** 57(5):209-216, 2002.

OBJETIVOS: Determinar os níveis séricos do fator reumatóide-imunoglobulina E na artrite reumatóide juvenil e correlacioná-los com parâmetros clínicos e laboratoriais.

MÉTODOS: Estudo multicêntrico prospectivo, realizado entre janeiro de 1993 a janeiro de 1999 com participação de três centros de reumatologia pediátrica. Estudaram-se 91 crianças com o diagnóstico de artrite reumatóide

juvenil de acordo com os critérios do Colégio Americano de Reumatologia: 38 (42%) com a forma de início sistêmica, 28 (31%) pauciarticular e 25 (27%) poliarticular. A idade variou de 2,1 a 22,6 anos (média de $10,5 \pm 4,7$ anos) e 59 (65%) crianças eram do sexo feminino. O grupo controle constituiu-se de 45 crianças saudáveis. A detecção do fator reumatóide-imunoglobulina E foi realizada através de um ensaio imunoenzimático. Associações do fator reumatóide-imunoglobulina E com: fator reumatóide-imunoglobulina M (látex), imunoglobulina E sérica total, VHS, FAN, classe funcional e radiológica III ou IV foram analisadas.

RESULTADOS: Das 91 crianças com artrite reumatóide juvenil, quinze (16,5%) apresentaram fator reumatóide-imunoglobulina E positivo. Destas, 7(18,5%) na forma sistêmica, 5 (18%) na pauciarticular e 3 (12%) na poliarticular. Observou-se correlação estatisticamente significativa entre o fator reumatóide-imunoglobulina E e a média geométrica da imunoglobulina E sérica total no total dos pacientes com artrite reumatóide juvenil; não foi observada correlação estatística entre o fator reumatóide-imunoglobulina E e positividade para o Látex, VHS, FAN e classe funcional e radiológica 3 ou 4 em nenhuma das formas de início da do-

ença. Dos 45 controles, 4 (8,9%) também apresentaram fator reumatóide-imunoglobulina E positivo, mas não houve correlação com a imunoglobulina E sérica total.

CONCLUSÕES: O fator reumatóide-imunoglobulina E pode ser detec-

tado em 16,5% dos pacientes com artrite reumatóide juvenil, especialmente naqueles com níveis elevados de imunoglobulina E sérica total. O fator reumatóide-imunoglobulina E parece não se associar com atividade ou gra-

vidade da artrite reumatóide juvenil.

DESCRITORES: Fator Reumatóide. Imunoglobulina E. Artrite Reumatóide Juvenil. Ensaio imunoenzimático.

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