J Pediatr (Rio J). 2015;91(4):352–357

Jornal de Pediatria
www.jped.com.br

ORIGINAL ARTICLE

Association of neopterin as a marker of immune system activation and juvenile rheumatoid arthritis activity☆

Mones M. Abu Shady[a], Hanan A. Fathy[b], Alaa Ali[a], Eman R. Youness[c,*], Gihan A. Fathy[a]

[a] *Child Health Department, Medical Division, National Research Centre, Cairo, Egypt*
[b] *Research Department, National Centre for Radiation Research and Technology, Atomic Energy Authority, Cairo, Egypt*
[c] *Medical Biochemistry Division, National Research Centre, Cairo, Egypt*

Received 13 March 2014; accepted 10 September 2014
Available online 26 February 2015

KEYWORDS
MCP-1;
TNF-α;
Rheumatoid arthritis

Abstract
Objective: To evaluate neopterin plasma concentrations in patients with active juvenile idiopathic arthritis (JIA) and correlate them with disease activity.
Methods: Sixty patients diagnosed as active JIA, as well as another 60 apparently healthy age- and gender-matched children as controls, were recruited from the Pediatrics Allergy and Immunology Clinic, Ain Shams University. Disease activity was assessed by the Juvenile Arthritis Disease Activity Score 27 (JADAS-27). Laboratory investigations were performed for all patients, including determination of hemoglobin concentration (Hgb), erythrocyte sedimentation rate (ESR), and C-reactive protein. Serum concentrations of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and neopterin were measured.
Results: Significant differences were found between JIA patients and controls with regard to the mean levels of Hgb, ESR, TNF-α, IL-6, and MCP-1 ($p < 0.05$). A statistically significant higher mean level serum neopterin concentration ($p < 0.05$) was found in JIA patients (20.43 ± 8.73 nmol/L) than in controls (6.88 ± 2.87 nmol/L) ($p < 0.05$). Positive significant correlations were detected between serum neopterin and ESR, TNF-α, IL-6, MCP-1, and JADAS-27 ($p < 0.05$). No correlation was found between serum neopterin and CRP ($p > 0.05$). Multiple linear regression analysis showed that JADAS- 27 and ESR were the main variables associated with serum neopterin in JIA patients ($p < 0.05$).
Conclusion: The elevation of plasma neopterin concentrations in early JIA patients may indicate stimulation of immune response. Serum neopterin can be used as a sensitive marker for assaying background inflammation and disease activity score in JIA patients.

☆ Please cite this article as: Abu Shady MM, Fathy HA, Ali A, Youness ER, Fathy GA. Association of neopterin as a marker of immune system activation and juvenile rheumatoid arthritis activity. J Pediatr (Rio J). 2015;91:352–7.

* Corresponding author.
E-mail: hoctober2000@yahoo.com (E.R. Youness).

http://dx.doi.org/10.1016/j.jped.2014.09.007

PALAVRAS-CHAVE
MCP-1;
FNT-α;
Artrite reumatoide

Associação de neopterina como marcador de ativação do sistema imunológico e atividade da artrite reumatoide juvenil

Resumo
Objetivo: avaliar as concentrações plasmáticas de neopterina em pacientes com artrite idiopática juvenil (AIJ) ativa e correlacioná-las com a atividade da doença.
Métodos: Sessenta pacientes diagnosticados com AIJ ativa, bem como outras 60 crianças aparentemente saudáveis com a mesma idade e sexo no grupo de controle, foram recrutados da clínica de Alergia e Imunologia Infantil da Universidade Ain Shams. A atividade da doença foi avaliada pelo Escore de Atividade da Doença da Artrite Juvenil em 27 Articulações (JADAS-27). Foram realizadas investigações laboratoriais em todos os pacientes, incluindo a determinação da concentração de hemoglobinas, a taxa de sedimentação de eritrócitos e a proteína C-reativa. Foram mensuradas as concentrações séricas do fator de necrose tumoral alfa, interleucina-6 e proteína quimiotática de monócitos-1 e neopterina.
Resultados: Foi encontrada uma diferença significativa entre os pacientes com AIJ e os controles quanto às médias de Hb, TSE, FNT-α, IL-6 e MCP-1 ($p < 0,05$). Foi encontrado um nível estatística e significativamente maior de concentração média de neopterina sérica ($p < 0,05$) em pacientes com AIJ (valor médio de $20,43 \pm 8,73$ nmol/L) que em controles (valor médio de $6,88 \pm 2,87$ nmol/L) ($p < 0,05$). Foram detectadas correlações positivas significativas entre a neopterina sérica e a TSE, FNT-α, IL-6, MCP-1 e JADAS-27 ($p < 0,05$). Não foi encontrada nenhuma correlação entre a neopterina sérica e a PCR ($p > 0,05$). A análise de regressão linear múltipla mostrou que o JADAS-27 e a TSE foram as principais variáveis associadas à neopterina sérica em pacientes com AIJ ($p < 0,05$).
Conclusão: A elevação das concentrações plasmáticas de neopterina em pacientes com AIJ precoce pode indicar um estímulo de resposta imune. A neopterina sérica pode ser usada como um indicador sensível para analisar o histórico de inflamações e o escore de atividade da doença em pacientes com AIJ.

Introduction

Juvenile idiopathic arthritis (JIA) is generally considered a clinical syndrome involving several disease subsets, with a number of inflammatory flows, leading to an eventual common pathway in which persistent synovial inflammation and associated damage to articular cartilage and underlying bone are present.[1] One main inflammatory process in the pathophysiology of the JIA consists of overproduction of tumor necrosis factor that leads to overproduction of many cytokines such as interleukin-6, which causes persistent inflammation and joint destruction.[2–4] The disease arises in a genetically susceptible individual due to environmental factors.[5] Moreover, it has been proposed that an antigen-driven autoimmune process mediates the inflammatory pathology in some cases of arthritis (e.g., oligoarthritis, polyarthritis). In contrast, there are no signs of lymphocyte-mediated, antigen-specific immune responses in individuals with systemic onset disease. Recent investigations in the pathophysiology of systemic onset disease have indicated that this disorder is due to an uncontrolled activation of the innate immune system.[6] Regardless of the differences in the underlying pathogenesis of the various types of JIA, pro-inflammatory cytokines are consistently overproduced and are related to the clinical manifestations in all types of JIA.[7]

The International League of Associations for Rheumatology (ILAR) classification system divides JIA into seven clinical subgroups.[8] The few population based estimates available indicate that the prevalence of JIA is approximately one to two per 1,000 children, and the incidence is 11 to 14 new cases per 100,000 children.[9]

Neopterin, a pyrazino-pyrimidine compound, is synthesized by monocytes and macrophages in response to interferon-γ (IFN-γ) produced by activated T-cells. It is a marker of cellular immune response, and levels are elevated in conditions of T-cell or macrophages activation, including autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis.[10,11]

The current study was undertaken to assess the association of plasma level of neopterin with inflammatory and disease activity in JIA patients.

Subjects and methods

The present study included 60 patients (30 males and 30 females) diagnosed as active JIA (Group 1) as well as 60 apparently healthy age- and gender-matched children as controls (Group 2). Patients were recruited from the Pediatrics Allergy and Immunology Clinic, Ain Shams University. Written informed consent was obtained from parents after explanation of the aim of the study. The protocol and all