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Review article

Intestinal parasites infection: protective effect in rheumatoid arthritis?☆

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ABSTRACT

Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease, with a progressive course, characterized by chronic synovitis that may evolve with deformities and functional disability, and whose early treatment minimizes joint damage. Its etiopathogenesis is not fully elucidated but comprises immunologic responses mediated by T helper cells (Th1). An apparent minor severity of RA in patients from regions with lower income could be associated with a higher prevalence of gut parasites, especially helminths. Strictly, a shift in the immune response toward the predominance of T helper cells (Th2), due to the chronic exposure to helminths, could modulate negatively the inflammation in RA patients, resulting in lower severity/joint injury. The interaction between the immunological responses of parasitic helminths in rheumatoid arthritis patients is the purpose of this paper.

Parasitoses intestinais: efeito protetor na artrite reumatoide?

Palavras-chave:
Artrite reumatoide
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RESUMO

A artrite reumatoide (AR) é uma doença inflamatória autoimune, sistêmica, de curso progressivo, caracterizada por exuberante sinovite crônica, que pode gerar deformidades e incapacidade funcional, cujo tratamento precoce minimiza o dano às juntas. Sua etiopatogenia ainda não está completamente elucidada, mas compreende respostas imunológicas com a participação de células T auxiliares (Th1). Uma aparente menor gravidade da AR

☆ Study conducted at the Rheumatology Department, Hospital Universitário de Brasília (HUB), Brasília, DF, Brazil.

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em pacientes de regiões com menor renda poderia estar associada a maior prevalência de parasitoses intestinais, especialmente as helmintíases. A rigor, um desvio na resposta imune para o predomínio de células T auxiliares (Th2), decorrente da exposição crônica a helmintos, modularia negativamente a inflamação em doentes com AR, e levaria a menor gravidade e dano articular. A revisão de aspectos da influência da reposta imunológica nas parasitoses intestinais, especialmente as helmintíases, em pacientes com artrite reumatoide é o objetivo desse trabalho.

Introduction

Rheumatoid arthritis (RA) is a chronic, progressive, systemic inflammatory autoimmune disease characterized by a symmetrical involvement of the synovial membrane of peripheral joints with joint damage and destruction.[1] Its prevalence is estimated at 0.2–1% of the population,[2] predominantly in women and with its highest incidence in the age group of 30–50 years.[1] RA is a multifactorial disease of unknown etiology, for which genetic (HLA-DR1 and HLA-DR4) and environmental (exposure to infections and smoking, among others) factors contribute for the loss of tolerance and organ damage.[3] If not treated properly, the disease can lead to functional limitations, with irreversible deformities and a reduced life expectancy.[1] The impact of RA is significant for both the patient (morbidity and mortality and decreased quality of life) and society (functional impairment with decreased productivity and lower capacity to participate in the labor market).[2]

Intestinal parasites infections include infections caused by protozoa and helminths with high morbidity and mortality. Their prevalence is estimated at 30% of the population of the Americas.[4,5]

Despite the morbidity and, less commonly, mortality that may be associated with parasitic infections, specifically in the case of helminths, subclinical infestations occur, which denounces an adaptation of the host to the parasite, with containment of damage and consequent survival of both sides. This host/parasite adaptation is related to components of the innate immune response and, in the case of the adaptive immune response, to the predominance of a Th2 response, with increased release of the so-called anti-inflammatory cytokines, such as interleukins (IL) 4, 10 and 13.[5]

In the literature, there are reports of lower prevalence and/or severity of RA in populations of sub-Saharan Africa; in our midst, a study conducted in Natal/RN, while addressing patients with systemic lupus erythematosus, found a similar level of severity in lupus patients versus populations of areas of greater economic power.[6] More recently, in a study on children with juvenile idiopathic arthritis cared for at a tertiary center in the state of Ceará, their authors found that about two-thirds of patients could achieve remission using methotrexate and/or leflunomide, despite the prevalence of the polyarticular subtype, which would have a worse prognosis.[7] The delays in establishing the diagnosis and in offering an early treatment, as well as the low family education/income found in our population, are factors considered as capable to aggravate the prognosis in autoimmune diseases. It is curious, therefore, that the long-term progression of these patients is at least equivalent, if not less severe, than that observed in populations with better socioeconomic indicators. This good response in potentially more severe patients, when compared to case series from rich countries of the Northern hemisphere, opens the possibility that environmental factors may be acting in the clinical course of autoimmune diseases.

The aim of this study is to elucidate the potential protective effect that the concomitant infection with intestinal parasites, especially helminths, could provide to patients with RA. In the period from May to July 2015, a literature review was carried out through Pubmed (1970–2015) and Scopus databases (English and Portuguese idioms), with the use of the following keywords: 'rheumatoid arthritis,' 'helminths,' 'immunopathogeny' and 'hygiene hypothesis'.

Immunopathogenesis of rheumatoid arthritis

The synovium or synovial membrane is considered as that tissue where the inflammatory process begins and perpetuates in RA, with the occurrence of a predominantly mononuclear inflammatory infiltrate, synovial hyperplasia and vascular proliferation associated with the production of proinflammatory cytokines. This hyperplastic synovium constitutes the synovial pannus that, through the invasion of the subchondral bone and underlying cartilage and also of tendons and ligaments, leads to joint destruction.[3,8] The basic mechanism proposed is the loss of immunological tolerance to self-antigens in a genetically susceptible individual, triggering synovitis.[3] In relation to mechanisms of the innate immune response, neutrophils, macrophages, mast cells and natural killer cells participate in this inflammatory response in the synovium.[3] Macrophages participate both in the role of antigen-presenting cells, as effector cells, through the release of the so-called pro-inflammatory cytokines (e.g. tumor necrosis factor (TNF)-α and IL-1β, IL-6, IL-12, IL-15, IL-18 and IL-23), reactive oxygen species, and production of prostanoids and extracellular matrix metalloproteinases.[3] It is assumed that TNF-α plays a central role in the pathogenesis of RA, promoting the release of other inflammatory mediators (i.e., cytokines with autocrine and paracrine action) and that the activation of lymphocytes and macrophages contribute to exacerbate the synovitis, besides promoting a direct activation of osteoclasts, which induce bone resorption.[3]

Classically, RA is described as an autoimmune disease mediated by T cells, especially effector Th1 and Th17 cells.[5,8]

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