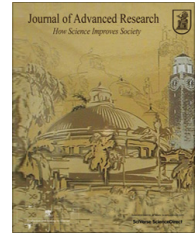




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# Development of rheumatoid arthritis during treatment of multiple sclerosis with interferon beta 1-a. Coincidence of two conditions or a complication of treatment: A case report



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## ABSTRACT

Coexistence of multiple sclerosis (MS) with other autoimmune diseases has been attributed to common background genetic or environmental factors. This study presents development of rheumatoid arthritis (RA) during treatment of MS. The MS was confirmed by the Mc Donald criteria and the diagnosis of RA was confirmed by the ACR/EULAR criteria. A 35 years old woman with 9 years of MS who was receiving interferon beta 1-a (INF) for 7 years and who did not respond to conventional therapy of RA over 8 months developed clinical manifestations of RA. But a rapid response was observed after discontinuation of INF. These findings suggest a possible contribution of INF in the development of RA.

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## Introduction

Patients with autoimmune diseases such as multiple sclerosis (MS) have greater susceptibility for development of another autoimmune disease [1–3]. This issue is important, because

occurrence of another condition, in particular a musculoskeletal disease in patients with previous neurologic lesions due to MS, increases the risk of disability. Occurrence of rheumatoid arthritis (RA) in MS may indicate coincidence of two conditions or a consequence of medical treatment. We report a case of MS who developed RA during treatment with interferon beta 1-a (INF) and response to conventional therapy was observed only after discontinuation of INF.

## Case presentation

A thirty-five years old woman was admitted to our hospital with polyarthritis involving wrists, right knee, metatarsal (MTP) and proximal interphalangeal (PIP) joints, morning

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stiffness to our hospital. Joint involvement and pain started two years prior to admission with an initial presenting manifestation of inflammatory arthritis [4,5]. Serologic assessment for rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (Anti-CCP) was negative at that time. Treatment was started with non-steroidal anti-inflammatory drugs (NSAIDs) and subsequently with hydroxychloroquine and low dose prednisolone. The patient had history of MS for 9 years and the diagnosis was confirmed by the McDonald criteria based on clinical manifestations with compatible brain lesions on magnetic resonance imaging. Treatment with intramuscular interferon beta-1a (INF) was started once a week and the patients achieved remission and continued maintenance treatment. Joints manifestations occurred 7 years after occurrence of MS which continued over the follow-up period and progressed to symmetrical polyarticular arthritis with synovitis and joints swelling. Clinical examination revealed joint pain and swelling in all involved joints and anti-cyclic citrullinated peptide antibody (Anti-CCP) and rheumatoid factor (RF) were positive. A definite diagnosis of RA was confirmed according to 2010 ACR/EULAR criteria after excluding other inflammatory arthritis [4,5]. Methotrexate (MTX) 10 mg weekly was added to hydroxychloroquine 200 mg and prednisolone 5 mg/daily and MS treatment with INF continued. Over the 8-month follow-up period, arthritis deteriorated and clinical examination revealed severe polyarthritis involving PIP, MTP, wrists, knee and MTP joints in spite of taking 15 mg MTX per week, prednisolone 5 mg daily and hydroxychloroquine 400 mg/daily. Further clinical examination and laboratory tests ruled out other inflammatory arthritis and HLA DRB1\*04, \*10 test was positive. The dosage of prednisolone was increased to 10 mg daily and treatment of MS changed to glatiramer acetate at 3 subcutaneous injections per week. The patients responded to the treatment and the results of the latest follow-up examination two years after beginning of RA showed remission of both RA and MS.

## Discussion

This study indicates development of RA in women with previously diagnosed MS under treatment with INF. The diagnosis of RA was confirmed based on the ACR/EULAR classification criteria and exclusion of other inflammatory arthritis by appropriated clinical and laboratory tests. Although radiographic erosions suggestive of RA have not been investigated, nonetheless, seropositivity for both RF and ACCP, HLA DRB1\*04, \*10 positivity, symmetrical involvement of the small joints of upper and lower limb joints provide further supporting data in favour of RA.

The association of MS and RA has been reviewed by Tousirot et al. in 14 cases (85.7% females) with coexistent diseases in the majority of patients and the MS occurred prior to development of RA and had no influence on the course of RA. The course of RA in 8 patients was progressive and the remaining patients had relapsing remitting courses. None of these patients received INF [1].

Coexistence of MS and juvenile chronic arthritis has been also reported [6,7]. Mpfu et al., reported a coincidental occurrence of RA in a 59 years old man with longstanding MS. Definite diagnosis with compatible features of RA was

possible only after four years of follow-up period. The patient had not received INF [2,3].

Patients with MS are more prone for development of second autoimmune disease. This has been attributed to genetic background or contribution of environmental factors such as viruses [8].

Several mechanisms including molecular mimicry, dual T cell receptors (TCRs) and chimeric TCRs have been proposed for development of autoimmune diseases. Initiation of autoimmune diseases by infectious agents is attributed to dual activity of the T cells [9]. Both genetic and environmental factors such as viruses have been incriminated for development of autoimmune diseases including MS and RA [8,9]. Th17 cells and IL17 have an important role in the host defence against extracellular fungal and bacterial pathogens and play a critical role in the pathogenesis of multiple inflammatory and autoimmune disorders [10] particularly immune mediated inflammatory arthritis such as RA, spondyloarthropathies, MS, psoriatic arthritis and SLE [11,12]. Innate-derived IL-17 constitutes a major element in the altered immune response against self-antigens or perpetuation of inflammation [13]. These cells have a crucial role in the pathogenesis of autoimmune demyelinating diseases in both mice and humans [14]. In RA the level of IL-17 in the synovial fluid correlates with disease severity and anti-IL-17 therapy is effective treatment of RA [15,16] Depending on the microenvironment, Th17 cells can alter their differentiation programme to either protective or pro-inflammatory pathogenic cells [10].

In MS patients treatment with interferon beta-1a can increase TGF- $\beta$ 1 [6]. It was shown that in both latent and active RA, the level of TGF- $\beta$ 1 in synovial fluid is increased [17]. In addition, rapid response to treatment after discontinuation of INF suggests an association between INF therapy and development of RA.

Development of juvenile chronic arthritis during treatment of MS has been reported [3]. This issue may suggest alteration in Th17 cells differentiation programme by INF [15] However, regarding a prolonged interval period between beginning of MS and development of RA, coincidence occurrence of two diseases cannot be ignored. This issue requires further studies.

## Conflict of Interest

*The authors have declared no conflict of interest.*

## Compliance with Ethics Requirements

*All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.*

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