Reumatol Clin. 2013;9(3):136–141

Reumatología Clínica

www.reumatologiaclinica.org

Original article

Carotid atherosclerosis in patients with rheumatoid arthritis and rheumatoid nodules

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ARTICLE INFO

Article history:
Received 14 March 2012
Accepted 18 July 2012
Available online 28 December 2012

Keywords:
Atherosclerosis
Rheumatoid arthritis
Carotid plaque
Intima media thickness
Cardiovascular disease

ABSTRACT

Objective: To determine whether an association exists between the presence of rheumatoid nodules and thickening of the intima-media and plaque of the carotid artery, which is evidence of atherosclerosis.
Materials and methods: Observational, cross-sectional study of 124 patients with rheumatoid arthritis from a University Hospital clinic from 2005 to 2006. We divided the patients into 2 groups, 62 with rheumatoid nodules and 62 without rheumatoid nodules, matched for age and sex. Medical history, erythrocyte sedimentation rate, anti-cyclic citrullinated peptide, rheumatoid factor, and a high resolution doppler ultrasound of the carotid arteries were performed.
Results: Women comprised 89.5% of the patients. The prevalence of a carotid plaque was 57% in our population. The presence of a plaque was associated with age, arterial hypertension and abdominal circumference. Average intima-media thickness (IMT) in patients with a plaque was 0.085 cm (±0.02). There was no correlation between laboratory parameters and thickening of the intima-media of the carotid artery. Subcutaneous nodules were present in 33 (47%) of the 70 patients with a carotid plaque and in 29 (54%) of patients without a carotid plaque ($p = .471$).
Conclusions: We did not find an association between rheumatoid nodules and the presence of a carotid plaque and thickening of the intima-media of the carotid in patients with rheumatoid arthritis.

Aterosclerosis carotídea en pacientes con artritis reumatoide y nódulos reumatoides

Palabras clave:
Aterosclerosis
Artritis reumatoide
Placa carotídea
Espesor íntima media
Enfermedad cardiovascular

RESUMEN

Objetivo: Determinar si existe una asociación entre la presencia de nódulos reumatoides y el engrosamiento de la íntima-media y de placa de las arterias carótidas.
Materiales y métodos: Estudio observacional, transversal de 124 pacientes con artritis reumatoide del Servicio de Reumatología de un Hospital Universitario desde 2005 a 2006. Se dividieron los pacientes en 2 grupos, 62 con nódulos reumatoide y 62 sin nódulos reumatoides, pareados por edad y sexo. Se realizó una historia clínica completa, velocidad de sedimentación globular, medición de anticuerpos antipéptidos cíclicos citrulinados, factor reumatoide y una ecografía doppler de alta resolución de las arterias carótidas.
Resultados: Las mujeres comprendieron el 89,5% de los pacientes. La prevalencia de al menos una placa en las carótidas fue del 57% en nuestra población. La presencia de placa carotídea estuvo asociada a la edad, hipertensión arterial y circunferencia abdominal. El grosor promedio de la íntima-media en pacientes con placa carotídea fue 0,085 cm (± 0,02). No hubo ninguna correlación entre los parámetros de laboratorio y el engrosamiento de íntima-media de la arteria carótida. Los nódulos subcutáneos estuvieron presentes en 33 (47%) de los 70 pacientes con placas de carótida y 29 (54%) de los pacientes sin una placa carótida (p = 0,471).

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1699-258X/$ – see front matter
http://dx.doi.org/10.1016/j.reuma.2012.07.006

Conclusiones: No hemos encontrado una asociación entre nódulos reumatoides y la presencia de placa y/o el engrosamiento de la íntima-media de carótidas en pacientes con artritis reumatoide.

Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory, multisystemic, multifactorial, autoimmune disorder of unknown etiology that affects mostly diarthrodial joints.[1] RA has a prevalence of 1–2% in the general adult population. The greatest incidence occurs between 35 and 45 years of age with predominance in women of 3–1. It presents as a chronic, bilateral, symmetrical erosive polyarthritis with diverse extrarticular manifestations that affect tissues and organs such as peripheral nerves, blood vessels, the lung, eyes, heart, and spleen with the presence of rheumatoid nodules, anemia, and symptoms of systemic disease. Three types of clinical course are recognized in this disease: type I, a self-limited process; type II, a polycyclic variant; and type III, the most frequent, which is progressive and deforming.[2]

Since the 1980s, RA has been known to lower life expectancy,[3–8] with a mortality rate similar to that observed in patients with Hodgkin disease, diabetes mellitus, or cerebrovascular disease.[4] Life expectancy can decrease 4–7 years in men and 3–10 years in women, but a decrease of up to 18 years has been reported.[9] The mortality rate in patients with RA increases during the course of the disease with a tendency to accelerate after 15 years.[10]

The main causes of death are cardiovascular (37.4%), cerebrovascular (9.4%), and pulmonary diseases (10%), neoplasias (10.3%), and infections (15.2%).[6,9,11–21] This information is from hospital[22–28] and community studies[20,21] that confirm that mortality is due mainly to cardiovascular disease. The incidence of cardiovascular disease in RA patients is independent of traditional cardiovascular risk factors.[26,29–32] The underlying mechanism for this increase has not been elucidated. Cardiovascular mortality has been correlated with greater activity of the disease (increased erythrocyte sedimentation rate,[33] severe extra-articular manifestations,[34,35] rheumatoid factor seropositivity,[36] C-reactive protein,[36–38] and the presence of rheumatoid nodules). The inflammation that occurs in persons with RA has been suggested to accelerate the atherosclerotic process.[30,36]

Intima-media thickness of the wall of the common carotid artery measured by high resolution ultrasound is a safe, non-invasive, reproducible, clinically useful biomarker of early stage atherosclerosis that correlates with coronary involvement.[39] This measure has greater predictive power than cardiovascular risk factors.[40] Intima-media thickness in RA patients correlates with the duration and severity of the disease.[33,36,41]

The association between carotid atherosclerosis, confirmed by ultrasound, and inflammatory markers, such as erythrocyte sedimentation rate and C-reactive protein, is independent of age, sex, and cardiovascular risk factors such as hypercholesterolemia, systolic arterial hypertension,[42] diabetes mellitus,[43,44] and body mass index.[24,25]

In RA, rheumatoid nodules are considered a manifestation of more aggressive disease; patients with rheumatoid vasculitis are known to have twice the probability of developing rheumatoid nodules.[45,46] Therefore, we considered it important to evaluate the correlation between atherosclerotic carotid disease and the presence of a specific extra-articular manifestation of RA, nodules. Rheumatoid nodules are tissue tumors that are usually located subcutaneously and that can be found in diverse organs, including the eye, lung, heart and brain. They are present in 20–40% of patients with rheumatoid arthritis and are more frequent on extensor surfaces of the limbs such as the olecranon. Nodules vary in consistency from a soft, amorphous, completely mobile mass to a hard mass firmly attached to the periosteum. They differ in size from a few millimeters to several centimeters and are usually painless. Their histologic appearance is considered characteristic, although not completely pathognomonic. Development of nodules is mediated through effects on small arterioles and the resultant activation of complement and terminal vasculitis.

In addition, another interesting point is the effect of anti-tumor necrosis factor alpha therapy and the methotrexate on the progression of atherosclerosis in RA patients through the determination of carotid IMT by ultrasound. In fact, several studies have shown a reduction of carotid IMT in patients with active RA receiving this medication.[47,48] Therefore, this image method could be a very useful tool for regular assessment, monitoring and management of cardiovascular risk in this population.

Patients and methods

The participants were patients who met at least 4 American College of Rheumatology[49] criteria for RA and who also attended the Rheumatology Service of the Hospital Universitario "Dr. Jose Eleuterio Gonzalez" of the Universidad Autónoma de Nuevo León from August 2005 to July 2006. The selection of patients with rheumatoid nodules was not based on a consecutive sequence of attendance to the clinic, but on an intentional search for the presence of nodules. Patients with nodules were matched with RA patients that did not have rheumatoid nodules according to age and sex.

Enrolled patients were greater than 16 years of age and provided informed consent for participation. Pregnant patients or those with a history of carotid surgery were excluded.

Clinical evaluation included a complete medical history with determination of active rheumatoid arthritis inflammation using the criteria previously mentioned[50]; we also documented the presence of extra-articular manifestations. In order to find out a possible association between IMT and antirheumatic therapy, including methotrexate, biologic therapy (anti-TNF blockers), antimalarials, and steroids, we classified the time of exposition to antirheumatic drugs in categorical variable (0 = none, 1 = 1–6 months, 2 = 7–12 months, 3 = 1–3 years, 4 = 3–5 years, 5 = 5–7 years, 6 = 7–10 years, 7 = >10 years).

Patients filled out a validated self-applied questionnaire in Spanish, the Modified Health Assessment Questionnaire (MHAQ).[27] The following laboratory tests were performed: complete blood count, liver function tests, urinanalysis, blood chemistry, and lipid profile. Also, C-reactive protein, erythrocyte sedimentation rate, rheumatoid factor, and anti-cyclic citrullinated peptide (anti-CCP) antibody titer were measured.

To measure C-reactive protein, we used the Lafon Protex-CR (Laboratorios Lafon, S.A. de C.V., Mexico) latex agglutination technique, which determines and quantifies C-reactive protein in serum by an indirect method.[51] A test was positive when macroscopic agglutination, and a clear plate bottom comparable to a positive control at a dilution of 1:40, equivalent to a sensitivity of 1.0 mg/dL, occurred.

Erytrosedimentation rate (ESR) was determined using the Winthrobe method. The upper limit of normal adjusted for age was considered a significant result; for men it was obtained by dividing the patient's age by two, and in women, age plus ten divided by two.[51]