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Uveitis is associated with hypertension and atherosclerosis in patients with ankylosing spondylitis: A cross-sectional study

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ABSTRACT

Objectives: Uveitis is the most common extra-articular manifestation in patients with ankylosing spondylitis (AS), but the literature describing AS patients with a history of uveitis is limited. The objective was to examine if a history of uveitis in patients with AS is associated with increased disease activity and functional impairment and to investigate whether uveitis is associated with an increased frequency of cardiovascular comorbidities, defined here as hypertension and atherosclerosis.
Methods: Data were recorded cross-sectionally through patient interviews, blood samples, clinical examination, and questionnaires. Carotid plaques were identified by ultrasonography. AS disease activity and function were compared across categories of uveitis using ANCOVA analyses. Associations between uveitis and hypertension and atherosclerosis [atherosclerotic cardiovascular disease (CVD) and/or carotid plaque] were analyzed in multivariate logistic regression models.
Results: Of 159 patients with AS (61.6% male, mean age 50.5 years), 84 (52.8%) had experienced one or more episodes of uveitis. AS disease activity was higher in patients with a history of uveitis, statistically significant for functional impairment [Bath AS Functional Index (BASFI)] [mean difference (95% CI)] lnBASFI = 0.2 (0.0–0.3), $p = 0.05$. Patients with uveitis had an increased odds ratio [OR (95% CI)] for hypertension [3.29 (1.29–8.41), $p = 0.01$] and atherosclerosis [2.57 (1.15–5.72), $p = 0.02$].
Conclusions: AS patients with a history of uveitis had non-significantly higher disease activity and significantly higher functional impairment. A history of uveitis was associated with hypertension as well as atherosclerosis. These results may be important in identifying AS patients with elevated risk of CVD but should be confirmed in longitudinal cohorts.

Introduction

Ankylosing spondylitis (AS) primarily affects the spine, but peripheral arthritis and enthesitis are also disease features. Many patients experience related diseases such as uveitis, psoriasis, and inflammatory bowel disease [1]. Uveitis is the most common extra-articular manifestation, affecting approximately 30% of the patients, and the prevalence correlates with disease duration [1]. Risk of uveitis is related to HLA-B27 positivity [2,3]. Despite the high occurrence of uveitis in AS, knowledge on associations between a history of uveitis and AS disease activity, functional impairment, and co-morbidities is limited.

AS patients have an increased prevalence of cardiovascular (CV) co-morbidities such as valvular defects and conduction disturbances and also of hypertension and atherosclerotic cardiovascular disease (CVD) [4,5]. However, it remains unclear whether all AS patients have an increased risk of CVD or if it is related to specific subgroups.

The aim of this study was to examine if AS patients with a history of uveitis have higher disease activity and functional

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impairment compared to AS patients with no history of uveitis and to examine whether AS patients with uveitis have a higher frequency of CV co-morbidities.

Methods

Design and patients

This was a cross-sectional study of hospital-recruited AS patients. The patients were identified from medical records at Department of Rheumatology at Diakonhjemmet Hospital in Oslo through having an AS diagnosis according to the modified New York criteria [6]. Most of the patients were recruited from the outpatient clinic. All patients were recruited from the Oslo area in Norway where the majority of the population are Caucasians with a Norwegian origin. Data were collected during the period 2008–2009. The study was approved by the Regional Committee of Medical and Health Research Ethics and performed according to the Helsinki declaration. The patients signed a written consent.

Study variables

Information on uveitis history, demographics, co-morbidities, and medications were self-reported in questionnaires.

Disease activity was assessed by the AS Disease Activity Score (ASDAS)-CRP and by Bath AS Disease Activity Index (BASDAI) [7,8]. Functional impairment was assessed by Bath AS Functional Index (BASFI) and Bath AS Metrology Index ($BASMI_{10}$) [9,10]. The latter was assessed by a physiotherapist. Disease duration was defined from onset of first symptoms.

Information on hypertension or history of CVD (angina pectoris, myocardial infarction, transitory ischemic attack, cerebral infarction, and intermittent claudication) was confirmed during a consultation with a cardiologist (A.G.S.). Atherosclerotic carotid plaques were assessed by B-mode ultrasonography examinations using a GE Vivid 7 ultrasound scanner (GE Vingmed Ultrasound, Horten, Norway) with a 12 (9-14)-MHz linear matrix array transducer. Plaques in the common carotid artery, bulb, and the internal carotid artery in the far and near wall were identified as protrusions into the lumen ≥ 1.5 mm or a protrusion >2 times the intima media thickness and were verified by a cross-sectional image obtained by rotating the probe 90°. Atherosclerosis was defined as having carotid plaque, history of CVD, or both.

Brachial blood pressure (BP) was measured after at least 5 min rest in a supine position using the OMRON M7 (Kyoto, Japan). Measurements were repeated until two differed by ≤ 5 mmHg in both systolic and diastolic pressure and the average was calculated. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2).

Blood samples were drawn after at least 4 h of fasting, and the following were analyzed: erythrocyte sedimentation rate (ESR) (mm/h) by the Westergren method, C-reactive protein (CRP) (mg/l), total cholesterol (mmol/l), and high-density lipoprotein (HDL) (mmol/l) by COBAS 6000 (Roche Diagnostic, Basel, Switzerland). Low-density lipoprotein (LDL) (mmol/l) was calculated from the Friedewald's formula [11]. Information on HLA-B27 was obtained from medical records.

Statistical analyses

We compared the demographics of patients with and without uveitis using Student's *t*-test, Mann–Whitney *U*-test, and chi-square test/Fisher's test as appropriate.

Associations between disease activity as well as functional impairment and uveitis were analyzed using age- and gender-adjusted ANCOVA with ASDAS, BASDAI, BASFI, and $BASMI_{10}$ as dependent variables and uveitis as the independent variable. BASFI and $BASMI_{10}$ were skewed and log-transformed to obtain normality. Analyses were performed both with adjustment for use of tumor necrosis factor alpha (TNFα)-inhibitors and with exclusion of patients using TNFα-inhibitors. Confounders [smoking (current and ever-never), HLA-B27] were added to the models consecutively.

Unadjusted associations between a history of uveitis, hypertension, and atherosclerosis were examined by the chi-square test. We introduced the following variables separately in age- and gender-adjusted univariate logistic regression models with hypertension/atherosclerosis as dependent variable: uveitis, HLA-B27, education >12 years, current smoking, ASDAS, CRP, use of TNFα-inhibitor, and non-steroidal anti-inflammatory drugs (NSAIDs). Variables with a p value ≤ 0.25 were included in a backwards multivariate logistic regression model. Non-significant variables from the adjusted univariate analyses were re-entered into the model to check for confounding/co-linearity. We then examined possible interactions between ASDAS and uveitis. The fit of the final model was assessed by the Hosmer–Lemeshow test.

To analyze the robustness of the results, traditional CVD risk factors [systolic BP, hypertension (atherosclerosis model only), total cholesterol, HDL, BMI, hypertension, and diabetes] were entered into both models.

Results

Out of 159 patients (61.6% male, mean age 50.5 years) with AS, 84 (52.8%) had experienced one or more episodes of uveitis. Cross-sectional comparisons of patients with and without uveitis are shown in Table 1. Patients with uveitis had significantly higher BASFI and $BASMI_{10}$ and longer disease duration. They had significantly more hypertension, atherosclerosis, and CVD and were more frequently using antihypertensive and TNFα-inhibitors.

Disease activity and functional impairment

The estimated differences (95% confidence interval) between uveitis and no uveitis for disease activity and functional impairment (after adjustments for age, gender, and use of TNF-inhibitors) were as follows: ASDAS = 0.3 (0.0–0.6), $p = 0.09$; BASDAI = 0.5 (−0.1 to 1.1), $p = 0.09$; lnBASFI = 0.2 (0.0–0.3), $p = 0.05$; $\ln BASMI_{10} = 0.1$ (−0.1 to 0.2), $p = 0.38$ (Fig. 1). The burden of disease was generally higher for uveitis patients but only reached statistical significance for lnBASFI. Adjustments for the confounders or excluding patients on TNFα-inhibitors did not alter results (data not shown).

Co-morbidities

Figure 2 shows the distribution of patients with uveitis, hypertension, and/or atherosclerosis. The figure indicates associations between uveitis and hypertension ($p = 0.004$), uveitis and atherosclerosis ($p = 0.003$), and also between hypertension and atherosclerosis ($p < 0.001$). In the multivariate logistic regression models, patients with a history of uveitis had a significantly increased odds ratio (OR) both for hypertension (OR = 3.29, $p = 0.01$), and atherosclerosis (OR = 2.57, $p = 0.02$), independent of other factors (Table 2). None of the other variables were significantly associated with hypertension and atherosclerosis. There were no significant interactions between uveitis and ASDAS.