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Description and Prevalence of Spondyloarthritis in Patients with Anterior Uveitis

The SENTINEL Interdisciplinary Collaborative Project

*Xavier Juanola, MD, PhD,[1] Estíbaliz Loza Santamaría, MD,[2] Miguel Cordero-Coma, MD, PhD,[3,4] for the SENTINEL Working Group**

Purpose: To describe and analyze the prevalence of spondyloarthritis (SpA) in patients with anterior uveitis (AU).

Design: Multicentric, observational, prospective study.

Participants: Consecutive patients with AU who were human leukocyte antigen (HLA)-B27 positive or HLA-B27 negative with more than 1 episode of AU separated by at least 3 months were selected. Patients with a previous diagnosis of SpA were excluded.

Methods: Included patients were evaluated by an ophthalmologist and a rheumatologist following a predefined visit schedule.

Main Outcome Measures: Sociodemographic and clinical variables including the diagnosis of SpA according to Assessment of SpondyloArthritis International Society (ASAS) criteria and an exhaustive ophthalmological examination (best-corrected visual acuity, intraocular pressure, biomicroscopic examination of the anterior and posterior segment of the eye, cataract evaluation, optical coherence tomography evaluating both the 1-mm central retina thickness and the optic nerve head and retinal nerve fiber layer, and visual field in a dark room with 1 eye patched) were collected. Baseline descriptive, bivariate, and concordance analyses were performed.

Results: We included 798 patients, mostly men (59%) with a mean age of 45 years; 60% were AU HLA-B27 positive, and 40% had recurrent negative AU HLA-B27. A total of 50.2% and 17.5% of patients presented axial and peripheral SpA according to ASAS criteria, respectively. Patients with AU who were HLA-B27 positive were more frequently diagnosed with axial (69.8% vs. 27.3%, $P < 0.0001$) and peripheral SpA (21.9% vs. 11.1%, $P < 0.0001$) than patients with recurrent negative AU HLA-B27. In general, we did not detect important differences between groups in the ophthalmologic variables.

Conclusions: A large percentage of patients with clinically significant AU have an undiagnosed SpA. This percentage is even higher if the HLA-B27 haplotype is positive. *Ophthalmology 2016;■:1–5 © 2016 by the American Academy of Ophthalmology.*

*Supplemental material is available at www.aaojournal.org.

Anterior uveitis (AU) is the most common form of intraocular inflammation, and approximately 50% of cases are associated with the human leukocyte antigen (HLA)-B27 allele. When AU is associated with HLAB27+, the risk for an underlying spondyloarthritis (SpA) is higher.[1]

However, uveitis is a frequent complication of SpA. The estimated prevalence of uveitis in SpA varies in up to one third of patients depending on the disease duration and SpA type.[2] The frequency of uveitis is greater in association with ankylosing spondylitis (AS) (20%–30%) than with inflammatory bowel disease (IBD) (2%–9%) or psoriasis (7%–16%).

Moreover, there might be differences according to SpA type. For example, the uveitis characteristic of AS (rapid onset, anterior, unilateral, recurrent, occurs more often in males) may differ from the phenotype often seen with psoriatic arthritis or IBD (insidious onset, anterior and intermediate, bilateral, chronic, or occurs more often in females).[3]

Although many cases of SpA usually are diagnosed in rheumatology units on the basis of other clinical findings such as inflammatory low back pain or arthritis,[4] Monnet et al[5] described that there could be patients with AU with an undiagnosed SpA. Therefore, an early recognition of a possible SpA in patients with uveitis attending an

http://dx.doi.org/10.1016/j.ophtha.2016.03.010
ISSN 0161-6420/16

ophthalmology unit is vital to improve these patients' management.

The aim of the SENTINEL project was to increase collaboration between ophthalmologists and rheumatologists to improve the management (and characterization) of patients with AU and the early detection of an underlying SpA.

Methods

Study Design

The SENTINEL project was an interdisciplinary, collaborative, multicenter, prospective study promoted by the Spanish Spondyloarthropathies Study Group of the Spanish Society of Rheumatology. For this purpose, a standardized protocol was generated. This project was approved by the ethics committee of one of the participating centers, and all patients signed the informed consent. A total of 66 centers (distributed throughout Spain) were recruited from October 2008 to February 2013.

Inclusion and Exclusion Criteria

We selected consecutive adult patients with anterior, noninfectious, clinically significant AU, diagnosed by an ophthalmologist, defined as an HLA-B27−positive haplotype with 1 or more episodes of AU or an HLA-B27−negative haplotype with more than 1 episode of AU separated by at least 3 months. Patients with a previous diagnosis of SpA or any other immune-mediated or infectious systemic condition were excluded. Patients with a clinical suspicion of having an infectious uveitis at the discretion of the investigator were excluded from the study.

Study Protocol

In each center, 1 rheumatologist and 1 ophthalmologist were responsible for the patients. Consecutive patients were included and evaluated by the ophthalmologist at baseline and at 3, 6, and 12 months, and at baseline and 12 months by the rheumatologist. Once the ophthalmologist confirmed inclusion criteria, patients were systematically referred to the rheumatologist. Other visits outside the schedule were allowed. For each visit, a specific set of variables to collect was defined. All data were collected and entered in the electronic platform by the 2 specialists.

The following variables were registered: (1) sociodemographics; (2) ophthalmological examination in all of the included patients[6]: best-corrected visual acuity, intraocular pressure measured in millimeters of mercury, biomicroscopic examination of the anterior and posterior segments of the eye,[7] cataract evaluation following the Lens Opacities Classification System III,[8] optical coherence tomography (Cirrus HD-OCT; Carl Zeiss Meditec, Dublin, CA) evaluating both the thickness of 1 mm of the central retina (using the macular cube strategy 512×128) and the optic nerve head and retinal nerve fiber layer using the optic disc cube strategy 200×200) (measured in micrometers), and visual field (baseline and 12 months) in a dark room with 1 eye patched with the proper refractive error trial lens using the Humphrey 24-2 SITA-fast protocol. Granulomatous uveitis (clinical appearance) was defined as those presenting with large, granulomatous (mutton-fat) keratic precipitates or iris nodules on the pupillary border or the iris surface. Fluorescein angiography was performed in patients with a clinical suspicion of having retinal vasculitis at the discretion of the investigator. Fluorescein angiography was performed at the baseline visit to determine the presence or absence of retinal angiographic leakage. Macular edema was defined as a central retinal thickness greater than 315 μm with demonstrated presence of intraretinal or subretinal fluid on optical coherence tomography.[9] In regards to a diagnosis of sarcoidosis, we did not systematically examine this diagnosis. However, in daily practice, ophthalmologic protocols usually include the serum concentrations of angiotensin-converting enzyme and a chest x-ray; (3) rheumatology data including all criteria for the diagnosis of axial or peripheral SpA according to the new Assessment of Spondyloarthritis international Society (ASAS) criteria,[10,11] Bath Ankylosing Spondylitis Disease Activity Index, and Bath Ankylosing Spondylitis Functional Index. The diagnosis of SpA was established by ASAS criteria and the rheumatologist's judgment.

Statistical Analysis

For the purposes of this study, we analyzed baseline data. To describe the sample, we used the distribution of frequencies, mean and standard deviation, or median and interquartile range, depending on the distribution. Comparisons were performed using the Student t test or chi-square test. The concordance between the rheumatologist's judgment and the new ASAS criteria in the diagnosis of axial and peripheral SpA was assessed with the Cohen's kappa coefficient. P values <0.050 were considered statistically significant.

Results

The study sample comprised 798 patients, most of whom were men (59%) with a mean age of 45±13 years (Table 1). A total of 475 patients (60%) were AU HLA-B27 positive, and 323 patients (40%) had recurrent negative AU HLA-B27.

At baseline, 77.8% of patients reported chronic back pain before age 45 years, and 44.1% of patients reported inflammatory back pain according to ASAS criteria. However, 60.4% of the study sample had a good response to nonsteroidal anti-inflammatory drugs, 35% of patients presented radiographic sacroiliitis, 12.7% of patients reported enthesitis of the heel, 3.4% of patients reported dactylitis, and approximately 12% of patients reported arthritis.

In the whole study population, 50.2% and 17.5% were diagnosed with axial and peripheral SpA according to the new ASAS criteria, respectively. Of note, 41% and 11.8% had axial and peripheral SpA, respectively, according to the rheumatologist's judgment. The agreement between the ASAS criteria and the rheumatologist's judgment was moderate. The kappa was 0.54 for the axial cases and 0.60 for the peripheral cases.

A total of 110 patients (13.8%) presented with bilateral concurrent AU at the baseline visit, of whom 39% were diagnosed with axial SpA and 14.5% were diagnosed with peripheral SpA according to the new ASAS criteria. Compared with those with unilateral AU, the rate of axial disease was significantly lower in the bilateral group ($P = 0.012$), but there were no statistically significant differences in the peripheral form of the disease.

In the subgroup of patients with axial SpA, 39.6% had nonradiographic SpA, 60.4% had AS, and they reported a mean Bath Ankylosing Spondylitis Disease Activity Index and Bath Ankylosing Spondylitis Functional Index of 2.92±2.28 and 2.53±2.29, respectively. Among those with peripheral SpA, 15% had psoriasis, 2% had an IBD, and 2.1% had a preceding infection.

When patients with AU were compared, patients who were HLA-B27 positive were somewhat younger than patients with recurrent negative AU HLA-B27 (mean age, 44 vs. 46 years; $P = 0.026$), and the percentage of men was significantly larger (67.4% vs. 47.4%; $P < 0.0001$). More patients in the HLA-B27−positive subgroup reported inflammatory back pain according to ASAS