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Seronegative spondyloarthropathies in Greece: a population-based study of prevalence, clinical pattern and management. The ESORDIG study

P Trontzas, A Andrianakos, S Miyakis, K Pantelidou, E Vafiadou, V Garantziotou, C Voudouris, for the ESORDIG study group

Authors' affiliations:

P Trontzas, A Andrianakos, K Pantelidou, E Vafiadou, V Garantziotou, Rheumatic Disease Epidemiology Section, Hellenic Foundation for Rheumatological Research, Athens, Greece.

S Miyakis, 3rd Department of Internal Medicine, Athens University Medical School, Sotiria Hospital, Athens, Greece.

C Voudouris, Department of Rheumatology, St. Paul's Hospital, Thessaloniki, Greece.

ABSTRACT

Objectives: To determine the prevalence, clinical pattern and management of seronegative spondyloarthropathies (SpA) in the adult general population of Greece.

Methods: This population-based study was conducted on a target adult (≥19-years-old) population of 14,233 subjects by rheumatologists who visited households in nine dispersed areas. An interview (standardized questionnaire) was conducted, clinical evaluation and laboratory investigation were done and established diagnostic classification criteria were used.

Results: The age- and sex-adjusted prevalence ($prevalence_{asa}$) of SpA was 0.49% (95% confidence interval [CI] 0.38-0.60), with a male to female ratio of 5.5:1; the prevalence increased with age until the 59-68-year-old age group and declined thereafter. The $prevalence_{asa}$ of ankylosing spondylitis (AS) and psoriatic arthritis (PsA) was 0.24% (95% CI 0.16-0.32) and 0.17% (95% CI 0.10-0.24), respectively. The mean age (yr) at onset was younger in AS (25.83±6.5) than in PsA (45.24±12.94), ($p<0.01$). Familial clustering was noticed in 5.3% of AS probands. Sacroiliitis was observed in 39.8% and asymmetrical oligoarthritis in 40.6% of PsA patients. Fifty-nine percent of SpA patients had previously visited rheumatologists (91.3% diagnosed correctly versus 11.6% of those who visited other specialists, $p<0.0005$); 56.5% of the former had taken disease-modifying antirheumatic drugs, compared to none of the latter.

Conclusions: SpA in Greeks are as common as in other European Caucasians, with a high male preponderance. PsA onset occurs at an older age than AS and frequently presents with a spondylitic pattern. The correct diagnosis was arrived at and appropriate treatment was given when patients consulted rheumatologists.

Keywords Ankylosing Spondylitis · Greece · Prevalence · Psoriatic Arthritis · Seronegative Spondyloarthropathies

Abbreviations SpA Seronegative Spondylarthropathies · AS Ankylosing Spondylitis · PsA Psoriatic Arthritis · ReA Reactive Arthritis · IBD-aA Inflammatory Bowel Disease-associated Arthritis · uSpA Undifferentiated Spondyloarthropathy · ESORDIG Epidemiological Study Of the Rheumatic Diseases In Greece · ESSG European Spondyloarthropathy Study Group · CI Confidence Interval; prevalence$_{asa}$ age- and sex-adjusted prevalence · NSAIDs onsteroidal ùnti-inflammatory Drugs · DMARDs Disease-Modifying Antirheumatic Drugs

Introduction

Seronegative spondyloarthropathies (SpA) are a group of chronic inflammatory rheumatic diseases affecting the spine and/or peripheral joints and periarticular structures and they are frequently associated with HLA-B27. SpA includes ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), inflammatory bowel disease-associated arthritis (IBD-aA) and undifferentiated spondyloarthropathy (uSpA).

The overall prevalence of SpA has been estimated in population-based surveys around the world to range from 0.0095% [1] to 2.5% [2]; scant data are available from southern Europe [3,4].

We present herein the data of a part of the ESORDIG (epidemiological study of the rheumatic diseases in Greece) [5], regarding the prevalence of SpA, the clinical pattern and the management care that was offered to these patients.

Materials and methods

Study population and subject evaluation

The ESORDIG was a cross-sectional population-based study, conducted on a target adult (≥19-years-old) population of 14,233 individuals. The study population consisted of all of the residents in seven areas dispersed in mainland Greece (8,547 subjects), as well as 2,100 out of 5,686 randomly selected subjects in one additional rural and one suburban area. In the latter areas every 2nd and 3rd household, respectively, was selected from a randomly chosen starting point: this was for practical reasons since there were only two available investigators for the suburban and one for the rural area. Thus, the final target population of the study was 10,647 individuals [5]. The number of families in the target population was 4,629 and the mean number of adult members in each family was 2.3 individuals. Sixteen rheumatologists conducted the survey by visiting the households of the final target population interviewing the study participants. Further data concerning the study population, subject evaluation, quality control and protocol approval are included in the first publication of the above study [5].

The interview which aimed at revealing subjects potentially suffering from SpA was based on a standardized questionnaire which consisted of two questions: 1) Have you ever had pain, swelling or stiffness, not due to trauma in any joint? 2) Have you ever had

low back pain or back stiffness on awakening which lasted over a period of at least 3 months, and which improved with exercise? Subjects who responded positively to either of these questions, were subsequently evaluated by the investigators (medical history, clinical examination, consideration of available laboratory and imaging findings), during the same visit. When necessary, appropriate x-ray investigation and/or other requisite laboratory tests were performed during the following days, and the findings were assessed by the investigators during a second visit in order to reach a definite diagnosis.

The diagnosis of SpA, either active or in remission, was made on the basis of the ESSG criteria [6]. Cases were further classified as AS when they met the modified New York criteria [7]. PsA was diagnosed if the ESSG criteria were fulfilled and typical skin or nail lesions were present. The diagnosis of ReA was based on a documented prior urogenital or gastrointestinal infection, while that of IBD-aA, on the presence of Crohn's disease or ulcerative colitis. Cases that met the ESSG criteria but did not fulfill diagnostic criteria for any specific SpA were considered as uSpA. An SpA patient with axial involvement was considered to be an individual with either sacroiliitis on x-ray or inflammatory back pain on clinical evaluation.

The effectiveness of the standardized questionnaire (responding positively to either of the two specific questions) was evaluated prior to the start of the study. Sensitivity was tested on 30 patients suffering from known SpA (16 AS, 9 PsA, 2 ReA, 1 IBD-aA, 2 uSpA) who were recruited from the investigators' outpatient clinics. Specificity was assessed in the framework of a pilot study of the ESORDIG study on 300 individuals without rheumatic disease[5].

Information regarding disease duration, family history, medical specialities involved in patient care, previous or current diagnosis, examinations results and treatment of the disease, which had also been documented in the personal health booklet of each patient (representing an actual medical file), as well as diverse information related to socio-demographic characteristics, was obtained and recorded by the investigators during the interview which was based on the standardized questionnaire.

Statistical analysis

The study population was weighted in terms of sex and age to the total adult population of the studied areas. The Student t-test was used to compare mean values, while the comparison of prevalence was done by the x^2 test and a probability value of $p<0.05$ was considered significant; 95% confidence intervals (CI) were given where relevant.

Results

We studied 8,740 individuals (participation rate 81.2%) of whom 4,269 (48.8%) were men and 4,471 (51.2%) women, ≥19 years of age (mean age 46.95±17.74 years); thirty-one percent were residents in urban, 34% in suburban and 35% in rural areas [5]. The investigators visited 4,162 families (family participation rate 89.9%) and interviewed a mean of 2.1 adult members in each family (participation rate in each family 91.3%). The sensitivity and the specificity of the standardized questionnaire were 100% and 83%, respectively.

SpA was diagnosed in 39 individuals (32 males and 7 females), mean age 46.18±14.75 years (table 1). Thus, the crude prevalence of SpA (8,740 responders) was 0.45% (95% CI 0.31-0.59), while in the total target adult population (14,233 subjects) the age- and sex-adjusted prevalence ($prevalence_{asa}$) of SpA was 0.49% (95% CI 0.38-0.60). The $prevalence_{asa}$ of SpA was significantly higher among males (0.83%) compared to females (0.15%) in the total target population ($p<0.0005$), with a ratio of 5.5:1. The male to female ratio did not vary significantly in relation to the age at the onset of the disease (ratio 6:1 versus 5:1 among patients with disease onset later or earlier than 40 years of age, respectively). In general, the $prevalence_{asa}$ of SpA increased until the 59-68-year-old age group ($p<0.009$), and then decreased ($p<0.008$) since only one case was identified in the ≥69-year-old age group. With regard to the $prevalence_{asa}$ of SpA there was no significant difference among the urban, suburban and rural subpopulations nor between the selected and non-selected populations (data not shown).

The SpA group consisted of patients with AS (50.7%), PsA (34.8%), ReA (8.7%) and uSpA (5.8%). The most common disease was AS followed by PsA with a $prevalence_{asa}$ of 0.24% (95% CI 0.16-0.32) and 0.17% (95% CI 0.10-0.24), respectively. The $prevalence_{asa}$ was significantly higher ($p\leq0.001$) in males (0.43% in AS and 0.29 in PsA) compared to females (0.07% in AS and 0.06% in PsA), with a sex ratio of 6.1:1 in AS and 4.8:1 in PsA. The $prevalence_{asa}$ of PsA peaked between ages 49 and 68 years. The mean age at AS onset was 25.83±6.5 years and that of PsA, 45.24±12.94 years ($p<0.01$). The $prevalence_{asa}$ of ReA was 0.04% (95% CI 0.01-0.07). Three cases of uSpA were also found. No cases of IBD-aA were recorded.

We found only one man with AS, whose a first-degree relative suffered from the same disease but the latter individual was not a resident in the studied areas. Thus, the 'familiarity', that is the proportion of probands with relatives suffering from the same disease, was 5.3% in our AS patients.

SpA with axial involvement (sacroiliitis and/or inflammatory spinal pain) in the study population was observed at a prevalence of 0.34% (95% CI 0.24-0.44). Sacroiliitis was recorded in all AS and in 39.8% of PsA patients, while the percentage of patients who had had (past and/or current) peripheral involvement was 59.5 of AS and 95.5 of PsA cases. Peripheral arthritis in PsA showed a pattern of asymmetric oligoarthritis in 40.6% patients, symmetric polyarthritis (rheumatoid-like) in 25.4%, and of distal interphalangeal joints in 29.6%.

wo patients with a disease duration of 31 and 11 years, respectively, were diagnosed as having SpA by the investigators. Although the other 37 SpA patients had sought prior medical assistance for their symptoms, at their first medical visit only 5 had consulted a rheumatologist and the remaining 32 had seen other physicians (Figure 1). Prior to the study, a total of 16 patients (41%) with SpA had never seen a rheumatologist (7 AS, 6 PsA, 1 ReA and 2 uSpA patients). A correct diagnosis was significantly more frequent when it was done by rheumatologists in comparison to other physicians (Table 2). Nonsteroidal anti-inflammatory drugs (NSAIDs) were the most frequently prescribed medication while disease-modifying antirheumatic drugs (DMARDs) were administered only by rheumatologists; physical therapy was also advised principally by rheumatologists (Table 2). All of the patients who had taken DMARDs had peripheral arthritis and the medications were methotrexate in 3 PsA patients and 1 with AS,

sulfasalazine in 4 AS patients, 2 with ReA and 1 with uSpA, while 2 patients with PsA had taken a combination of methotrexate plus cyclosporine.

Discussion

Greece demonstrates ethnic homogeneity (98.3% of its population are Caucasian Greeks), and no important ethnic or racial differences exist between the various geographical departments. The study population was representative of the total Greek population in terms of age and sex distribution [5].

The published data reports a wide-range prevalence of SpA, and this, for a variety of reasons: methodological differences between the epidemiological surveys such as differences in the target population (e.g. adults versus total population), in the selection of the population (e.g. blood donors, population register, general practitioner register, hospital-based population), in the contact procedure with subjects (e.g. interview by medical doctors or by non-medical staff, telephone interview, post-questionnaire), as well as a different spectrum of diseases studied or different objectives (e.g. symptoms versus diseases). Additionally, diversity in the results could be a result of differences in the definition of the diseases or in the diagnostic criteria applied; in cases of SpA, the lack of a clear definition of some of the separate diseases (such as ReA, PsA, or uSpA), may be a reason for further bias.