Early spondyloarthritis: results from the pilot registry ESPIDEP

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Abstract

Objective

Studies on the incidence of spondyloarthritis (SpA) are scarce. Early SpA clinics should facilitate the detection of new cases as well as to decrease the diagnosis and treatment delay. However, the workload of such clinics has not been estimated.

Methods

ESPIDEP is a pilot registry of patients with early SpA performed in Madrid, Spain. General practitioners (GPs) agreed and were trained to refer all patients under 45 with either inflammatory back pain or asymmetric arthritis of lower limbs with 3 to 24 month duration of symptoms to a specialised unit during 6 consecutive months. Case definition of SpA was based on the ESSG criteria. The success of the program was measured by: the satisfaction of the GPs regarding the referral process, the percentage of patients correctly derived according to the rheumatologist, the expected incidence of AS.

Results

From a population of 111,941, the unit attended 52 patients, of whom 43 (83%) had been derived correctly and 35 were diagnosed with SpA (49% women; mean age 33±8; mean duration of symptoms 11±6 months; 46% HLA-B27 positive). The annual estimated incidence of SpA was 62.5 cases per 100,000 (95% CI: 45–87). Only 20/35 (57%) had radiological sacroiliitis and 4 (11.8%) fulfilled the modified New York criteria for ankylosing spondylitis (annual estimated incidence 7.2 per 100,000 (IC95%: 3.1-14.1)).

Conclusion

Around 60 cases of early SpA are expected annually in an area of 100,000. A referral based upon clinical parameters seems efficient. The planning of early SpA clinics may be based upon these figures.

Key words

Spondyloarthritis, ankylosing spondylitis, psoriatic arthritis, reactive arthritis, undifferentiated spondyloarthritis, epidemiology

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Introduction

Spondylarthritides (SpA) comprise a group of diseases which share clinical manifestations and an association with HLA-B27. The prevalence of SpA, as a group, is comparable to that of rheumatoid arthritis, and in Europe lies between 0.32 and 1.73% (1). The annual incidence of ankylosing spondylitis (AS) ranges between 0.5 and 8.2 per 100,000, very seemingly dependent on the rate of HLA-B27 in the background population (2). In fact, it has been described that prevalence of AS is increasing in the last years (3). Data on the frequency of SpA in our country are lacking. A nationwide epidemiological study on rheumatic diseases showed a prevalence of inflammatory back pain (IBP) of 0.8%, although the prevalence of SpA could not be specifically investigated (4), mainly because of the difficulty of performing sacroiliac radiographs on healthy subjects.

The most common subgroups of SpA are AS and undifferentiated spondyloarthritis (uSpA) (5), although, in principle, all forms of SpA may progress to full AS. The established classification criteria for AS rely on the combination of clinical symptoms plus unequivocal radiographic sacroiliitis (6) but x-rays are often normal when symptoms first arise, and the diagnosis of AS is commonly delayed several years after the onset of symptoms (7). In our setting, for instance, the diagnosis of AS is usually delayed 6 years after the disease begins (8).

The AS classification criteria are highly specific in established disease, but they are not useful for patients with early disease, and a new set of diagnostic criteria has now been published (9). Also, until recently, the therapeutic options for patients with AS and SpA were very limited. This perception has dramatically changed after the introduction of anti-TNF therapies, which have demonstrated to reduce disease activity, including metrologic parameters such as BASMI, Schöber's test, or chest expansion (10-12). In addition, some data suggest that anti-TNF therapies might alter the progression of spinal structural damage detected by magnetic resonance imaging (MRI) in patients with AS (13-15) although they may not alter progression of spinal diseases as measured by mSASSS (16) and they have been included in international recommendations early in the treatment of AS (17). Therefore, reducing the gap between the onset of SpA and its diagnosis is deemed crucial to improve outcome. Early disease clinics are a strategy deemed to improve diagnosis and treatment of patients in many diseases, including rheumatic ones (18). The pillar to an early clinic should be the justification of a better outcome if an early diagnosis and treatment are made, which seems the case in SpA. The establishment of any management unit, however, needs several initial steps, one being the estimation of the unit work-load. As a way to estimate the needs of a program for early arthritis, we designed a pilot study. The aim of such study was 1) to set up an efficient referral system to accelerate the diagnostic process of patients with SpA in our area, and 2) to estimate the incidence of SpA and therefore of the burden of an early SpA clinic. We called this study "ESPIDEP" ("*EStudio PIloto de Derivación de pacientes con Espondilartritis Precoz*", Pilot Study for the Referral of Patients with Early SpA).

Methods

This pilot program was carried out in Health District 5 of Madrid, Spain, an area of 787,000 covered by La Paz hospital. Eight Primary Care Centres (PCC) were selected for the pilot study, covering an area of 242,794 people. The program included protocols in all aspects related to the process of care in early SpA: referral criteria, training of the GPs, procedures in the clinic, feed-back of the GPs, diagnosis, treatment and follow-up of the patients. The study was approved by the Ethics Committee of La Paz Hospital in February 2006. The recruitment period started on February 1st and ended on July 31st, 2006.

Referral criteria

The referral criteria were proposed by the team of rheumatologists and agreed with the general physicians (GPs) who were to use them. The criteria were:

1) Age below 45, 2) Symptoms duration between 3 and 24 months, and 3) At least one of the following two: a) asymmetric arthritis of lower limbs OR b) inflammatory low back pain defined by at least two of the following: insidious onset, morning stiffness for more than 30 minutes, or clear improvement of the symptoms with physical activity. The criteria were printed in special referral forms and distributed among the GPs. The referral forms were then used to derive the patients to the specialised unit, where a rheumatologist checked the adequacy of the referral criteria marked.

Training of GPs

One of the rheumatologists in the study was responsible for the training sessions in the program. The sessions were held in each of the 8 PCC and all GPs in each centre were invited to participate. The content of the sessions included the justification, aims, and procedures of the program, as well as formal training on how to identify IBP, and on how to treat non-inflammatory low-back pain and on signs of alert. All GPs (n=109) signed a written commitment to participate in the study according to the established procedures and were provided with a dossier containing the protocol of the study, the referral forms, and the address and phone of the personnel in charge of setting the appointments with the rheumatologist of the Early SpA Unit.

Procedures in the Early SpA Unit

All procedures were applied to the patients who fulfilled the referral criteria, in spite of the diagnosis. Patients signed an informed consent upon the first visit at the Early SpA Unit. The procedures included confirmation of referral criteria, detailed medical history and examination, collection of specific SpA data, such as a numerical rating scale of global patient assessment, BASDAI and BASFI questionnaires, BASMI, chest expansion, the number of painful and swollen joints and the enthesis index. Laboratory and x-ray studies performed were: haematology, biochemistry, C-RP, ESR, HLA-B27 (by microlymphocytotoxicity assay (19) and by flow cytometry (20); HLA-B27 subtypes were determined using the PEL-FREEZ® SSP Unitry Kit (Dynal Biotech, Wisconsin, USA) (21)), rheumatoid factor, antinuclear antibodies, and radiographs of pelvis, neck, dorsal, and lumbar spine. An MRI was performed according to the decision tree algorithm proposed by Rudwaleit *et al*. in 2004 (22) and in other cases to confirm diagnosis.

Diagnostic criteria

The European Spondylarthropathy Study Group (ESSG) preliminary criteria for the classification of SpA (23) were used for diagnosis. Although these criteria were defined for classification and not for diagnosis, they were tested in early SpA (53 patients *vs*. 83 controls) and showed a sensitivity of 67.9% and specificity of 92.8% (23). In addition ESSG criteria were easy to use in clinical practice. For these reasons, the team of rheumatologists decided to use them for diagnosis.

For classification of AS, the New York modified criteria were used (6). Psoriatic arthritis and reactive arthritis were diagnosed by international established criteria (24, 25). A diagnosis of inflammatory bowel disease was made when the endoscopic and/or gut histology picture was characteristic.

Diagnosis was assessed as of the second visit, after all tests had been collected, between 15 days and a month after first visit.

Evaluation of the program

Once the period of inclusion was over, a short questionnaire was sent to all GPs to evaluate their satisfaction with the referral process. They were asked whether the referral process was adequate, useful, easy, and clear, by means of 5-point Likert scales. A final recommendation of the process was prompted (1, "absolutely not recommended" to 5 "absolutely recommended").

Additional indicators of the performance of the program were: 1) the percent of patients correctly derived, that is, the percentage of patients who fulfilled the referral criteria according to the rheumatologist; 2) the percentage of GPs in each PPC who attended the training sessions; and 3) whether the incidence of AS was within the limits estimated in previous studies.

Statistical analysis

We estimated the one-year cumulative incidence of SpA with 95% confidence intervals (95% CI) based on the number of patients, referred by the participating GPs who were diagnosed with any type of SpA during the recruitment period. The total population covered by the participating PPCs was 242,794; however, the age range of the patients according to inclusion criteria was 16 to 45 years. Thus, to calculate the incidence, we used as a denominator the 16-45 stratum (n=111,941). Data stratified by age group and gender were obtained from the participating PCC. The incidence was also estimated by diagnosis and by gender.

For the description of the patients, we used statistical descriptors adequate to the distribution of the variables. For the comparison of groups we used non-parametric tests, given the small sample size. All analyses were performed with Stata 10.0 (StataCorp LP; College Station, TX, USA).

Results

Incidence of early SpA

During the 6-month inclusion period, 52 patients were referred to the Early SpA Unit. According to the attending rheumatologist in the unit, 43 (82.7%) fulfilled the referral criteria. In 29 patients (67.4%), the referral criterion was IBP, in 7 (16.3%) it was asymmetric arthritis of the lower limbs, and both criteria were present in the remaining 7 (16.3%). After excluding two patients who were lost after the first visit, 39% percent had a positive HLA-B27. Of the 43 patients who fulfilled the referral criteria, 35 (67.3%) were finally diagnosed with some type of SpA, 6 had other diagnoses and 2 patients with IBP were lost to follow-up after the first visit (Table I).

The estimated annual incidence of SpA is 62.5 cases per 100,000 (95% CI: 44.9–87.0). In women, the incidence is 60.9 cases per 100,000 (95%CI: 37.8–97.9), and in men 64.2 cases per 100,000 (95%CI: 40.4–101.9). Table

Table I. Diagnoses made in the Early Spondyloarthritis Unit for patients correctly fulfilling the referral criteria. Percentage of men and of positive HLA-B27 in early SpA patients.

Diagnosis	n. (%)	Men n. (%)	B27+ n. (%)
Undifferentiated spondyloarthritis	26 (60.5)	14 (54)	11 (42)
Ankylosing spondylitis	4 (9.3)	1 (25)	3 (75)
Reactive arthritis	2 (4.6)	2 (100)	2 (100)
Psoriatic arthritis	2 (4.6)	0	0
Inflammatory bowel disease (ulcerative colitis)	1 (2.3)	1 (100)	0
Chronic non-specific back pain*	7 (16.3)	3 (42.9)	0
Villonodular synovitis	1 (2.3)	1 (100)	0
Total	43 (100)		

*Two patients did not have a further specific diagnosis since they were lost to follow-up.

Table II. Annual incidence of Early SpA, and of specific diagnoses, per 100,000. Madrid, Spain, 2006.

Diagnosis	n.	Incidence per 100,000	95% confidence interval
All spondyloarthritis	35	62.5	(44.9 - 87.0)
Undifferentiated spondyloarthritis	26	46.5	(31.6 - 68.0)
Ankylosing spondylitis	4	7.2	(2.7 - 19.0)
Psoriatic arthritis	2	3.6	(0.9 - 14.0)
Rective arthritis	2	3.6	(0.9 - 14.0)
Arthritis related to IBD*	1	1.8	(0.3 - 12.0)

IBD: inflammatory bowel disease

Table III. Clinical features of patients who fulfilled the referral criteria and then of those who were diagnosed with SpA and of those who did not.

	All patients fulfilling referral criteria* (n=43)	SpA* (n=35)
Age	33.6 (8.75; 15-45)	33.7 (8.14; 15-45)
Duration of symptoms (months)	11.9 (6.7; 3-24)	11.2 (6.5; 3-24)
Number of SpA-related symptoms	2.65 (1.43; 1-7)	2.5 (1.29; 1-6)
Patient's global assessment (0-10)	4.9 (2.5; 0-9)	4.63 (2.6; 0-9)
BASDAI	4.6 (1.9; 1-9.2)	4.56 (1.99; 1-9.2)
Pain VAS (0-100 mm)	43.75 (36.14; 0-100)	44.36 (36.62; 0-100)
Morning stiffness (minutes)	25.95 (30.5; 0-120)	26.61 (33.16; 0-120)
Number of painful joints (46 joints)	0.62 (1.8; 0-11)	0.71 (2.01; 0-11)
Number of swollen joints (44 joints)	0.26 (0.49; 0-2)	0.26 (0.51; 0-2)
BASFI	2.7 (2.5; 0-10)	2.44 (2.38; 0-8)
BASMI	1.5 (0.87; 0-3.4)	1.48 (0.9; 0-3.4)
Number of painful enthesis	1.27 (3.49; 0-18)	1.48 (3.8; 0-18)
Chest expansion (cms)	5.31 (2.08; 2-10)	5.5 (2.18; 2-10)
ESR (mm/h)	17.85 (21.36; 1-90)	19.48 (23.6; 1-90)
C-reactive protein (mg/l)	12.13 (24.36; 0.4-109)	14.78 (27.18; 0.4-109)

*All results are expressed as mean (standard deviation; range).
VAS: visual analogue scale; ESR: erythrocyte sedimentation rate.

II shows the incidence rate by specific diagnoses.

Clinical features of patients with SpAs

Table III shows the characteristics of the correctly referred patients, of whom half were men with a mean age of 33. The mean duration of symptoms was 11 months and 45.7% were HLA-B27 positive. These percentages varied depending on the final diagnosis, as shown in Table I. Interestingly, 3 of the 4 patients with AS were women. HLA-B27 was present in the 2 patients with reactive arthritis and in a 75% of the patients with AS. Among the HLA-B27 positive patients, 90% had the HLA-B2705 subtype. All patients were negative for rheumatoid factor and antinuclear antibodies.

Plain radiography showed unilateral sacroiliitis in 11 patients (32.3% of SpA patients) and bilateral sacroiliitis in 8 (23.5%), although only 4 (11.8%) fulfilled the modified New York criteria for AS. Fifteen patients (42.9% of SpA) did not have sacroiliitis.

According to the decision tree algorithm proposed by Rudwaleit *et al*. (22), MRI was needed only in two patients, one finally diagnosed of undifferentiated SpA, that had not sacroiliitis on plain radiography, an one of Chronic unspecific lumbar pain. In both cases MRI did not show any abnormalitie.

As of the first visit to the clinic, women had a significantly higher number of swollen joints than men (0.5 versus 0.1; p=0.005). As Table III shows, early SpA patients show an active disease with high BASDAI scores, prolonged morning stiffness, and elevated CRP. On the contrary, function, spinal mobility, and radiographic scores seem well preserved.

Evaluation of the program

Out of the 109 GPs involved in the study, 33 (30.3%) responded to the satisfaction questionnaire. Two percent of physicians gave a level of recommendation of 3, 28% gave a level of 4 and 60% gave a level of recommendation of 5 (the strongest recommendation).

The percent of patients correctly derived was 82.7%, and the average percentage of GPs in each PPC who attended the training sessions 76%. The incidence of AS is within the expected frequency. GPs were adequately informed about the final result of the pilot program, as a ways of providing useful feed-back.

Discussion

Our study permits a close estimation of the work-load of an early SpA clinic attending patients derived directly from Primary Care. The dimension or burden of such a clinic should be based

in the incidence of early SpA, among other aspects. In this sense, an early SpA clinic should be prepared to follow around 62 new SpA cases per 100,000 in a year, and to receive about 75 referrals. However, we would like to emphasise that full cooperation between primary-care and specialist-care providers is essential to success in our pilot program. Had this been less close, the number of unwanted referrals may have been much larger and the number of new cases of AS, probably smaller.

Over the last few years, groups of rheumatologists have been trying to accelerate the early diagnosis and treatment of patients with SpA. Recommendations for early referral of AS in primary care and a diagnostic algorithm for pre-radiographic stages of axial SpA have been proposed. This algorithm is based on likelihood ratios for developing AS of SpA clinical parameters, HLA-B27, and MRI (22). However, its usefulness has not been proven in daily practice.

In Berlin, Sieper and Rudwaleit (26) have proposed, as referral criteria, the presence of low back pain for more than 3 months in patients under 45 plus a) IBP or b) HLA-B27 or c) presence of sacroiliitis (by x-ray or MRI). The results of the application of these referral recommendations in patients with chronic back pain has been proven to be useful, when applied in primary care, for identifying new patients with AS or pre-radiographic axial SpA with long standing disease of several years of duration (27). However, laboratory or imaging parameters may be costly or difficult to use in the primary care setting. This is the reason why we chose excluding any imaging or laboratory techniques from the referral criteria, in agreement with the GPs that were to derive the patients. Our results confirm that clinical referral criteria without laboratory tests or imaging procedures may be as efficient, as a more comprehensive referral criterion.

The second main experience in early SpA has been published from the Maastricht SpA clinic (28). In this study, patients referred had an IBP of less than 2 years duration (n=68). The source of patients' referral could either be rheumatologists, or orthopaedic surgeons, or dermatologists, or gastroenterologists, or ophthalmologists. The study compared three different criteria set for the diagnosis of SpA, being the ESSG criteria the most sensitive, then followed by Amor's, and Berlin's criteria. Out of the 68 patients with IBP, 56 fulfilled ESSG criteria, 48 Amor's criteria and 43 Berlin's criteria. Only 4 patients did not fulfil any criteria set and 36 (53%) fulfilled all criteria sets. In this cohort, the contribution of MRI – performed in all patients as per protocol – and of HLA-B27, was limited for making a diagnosis of axial SpA.

To our knowledge, our study is the first conducted in patients with early SpA where referral criteria were agreed upon by both GPs and rheumatologists. Our results showed three relevant facts, 1) GPs observed the referral criteria to a high degree (82.7%), 2) Up to 2/3 of the referred patients had a diagnosis of SpA and 3) The use of clinical criteria alone for referring patients is efficient in clinical practice. These results clearly derive from the good interaction between the rheumatologists and the GPs that participated in the ESPIDEP study. The composition of an early SpA clinic may differ from a clinic for established SpA. The ESPIDEP patients presented high disease activity but without clinically relevant functional or radiologic consequences. These characteristics, plus the high proportion of women (49%), and the low percentage of HLA-B27 positive patients (46%), are in accordance with those described at the Maastricht early SpA clinic (28) and in the MRI study in patients with early SpA (29), all in which support the idea that early SpA is clinically different than long-standing disease. A plausible explanation for these discrepancies might arise from the high level of alertness that leads to recruiting any suspected patient, not only those severely affected. Nonetheless, the sex ratio and the HLA-B27 distribution may depend on the type of SpA as shown in Table 1. The high predominance of the HLA-B2705 subtype (90%) agrees with previous data from our country (30).

In spite of the efforts to accelerate the diagnosis of AS, criteria for early diagnosis of this disease are still lacking. We used the ESSG criteria as a gold standard for the diagnosis of SpA. However, it should be emphasised that it has been described that only 50% of the patients who fulfil initially the ESSG criteria are usually still classified as SpA five years later (31).

This is the first study providing data about the incidence of SpA in our country, which was found to be 62.5 new cases per 100.000 persons per-year, with an incidence rate for AS of 7.2 per 100.000 persons per-year. Studies on the incidence of SpA and AS are scarce in the literature, but our results were in accordance to those found in other countries of Europe (2, 32). One point of criticism could be that some cases of early SpA could be missed during the study period. In this case, our incidence data could be under-estimated.

In conclusion, this is the first study to integrate GPs and rheumatologists in the early diagnosis of SpA. The proposed referral criteria were effective in detecting early SpA which was diagnosed in 2 out of 3 referred patients. In addition, this is the first study that attempted to approximate the incidence of SpA in our country. The clinical characteristics of early SpA patients may have some differences from those found in patients with long-standing disease such as a higher proportion of women and a lower percentage of positive HLA-B27. Our cohort of SpA patients had an active disease with low impact on both function and structural damage, suggesting that therapeutic intervention at this stage of the disease can be crucial in modifying outcomes.

Appendix

The ESPIDEP Study Group

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