

Undifferentiated spondyloarthritis is more frequently seen in women than in men

Sukran Erten^a, Orhan Küçükşahin^a, Ali Sahin^b, Nurdan Cay^c, Gulay G. Ceylan^d

^aDepartments of Rheumatology, ^bRadiology, ^cMolecular Genetics, Yıldırım Beyazıt University Atatürk Education and Research Hospital, Ankara, ^dDepartment of Rheumatology, Cumhuriyet University Education and Research Hospital, Sivas, Turkey

Correspondence to Orhan Küçükşahin, MD, Atatürk Eğitim ve Araştırma Hastanesi, Romatoloji Polikliniği, 06800 Ankara, Turkey
Tel: +90 312 291 2525/4125;
fax: +90 312 291 2705;
e-mail: orhankcs@gmail.com

Received 29 January 2015

Accepted 11 March 2015

The Egyptian Society of Internal Medicine
2015, 27:53–57

Introduction

Spondyloarthritis (SpA) are a group of inflammatory rheumatic diseases that share some common clinical and genetic features such as inflammatory back pain, peripheral arthritis, enthesitis, anterior uveitis, sacroiliitis, and HLA-B27 positivity. The aim of the present study was to describe the clinical, radiologic, and genetic features of patients with undifferentiated spondyloarthritis (uSpA) and ankylosing spondylitis (AS).

Patients and methods

This study included 225 SpA patients (134 uSpA and 91 AS) attending our Rheumatology Outpatient Clinic consecutively. Patients underwent peripheral and axial joint and enthesitis assessment, erythrocyte sedimentation rate or C-reactive protein determination, HLA-B27 tissue typing, radiographic evaluation, and sacroiliac MRI.

Results

In total, 26 of 91 AS patients and 115 of 134 uSpA patients were women (28.6 vs. 85.8%) and 65 of AS and 19 of uSpA were men (71.4 vs. 14.2%). The time for diagnosis was 15.82 ± 20.7 months for AS patients and 5.91 ± 3.63 months for uSpA patients. Diagnostic delay was 102.46 ± 88.99 (median 83, range 8–377) months for AS and 74.23 ± 60.7 (median 55.5, range 0–238) months for uSpA patients. HLA-B27 positivity was present in 51.6% of AS and 14.9% of uSpA patients. The mean BASDAI level of patients with AS was 6.4 ± 1.1 and that of uSpA patients was 4.8 ± 2.1 .

Conclusion

SpA are frequent diseases and physicians other than rheumatologists should also be aware of them. uSpA is more frequent in women than men. Early diagnosis of SpA is important because early treatment with new biological therapies may lead to much better results than applying them in the advanced stages.

Keywords:

ankylosing spondylitis, axial spondyloarthritis, HLA-B27, sacroiliac MRI, spondyloarthritis

Egypt J Intern Med 27:53–57

© 2015 The Egyptian Society of Internal Medicine
1110-7782

Introduction

The inflammatory rheumatic diseases affecting the axial spine are included in the group of spondyloarthritis (SpA) [1]. The SpA concept comprises ankylosing spondylitis (AS), psoriatic arthritis, arthritis/spondylitis with inflammatory bowel disease (IBD), and reactive arthritis. SpA are frequent diseases. In a recent study from Turkey, the prevalence of AS was found to be 0.49 and 1.05% for the all SpA [2]. They are characterized by the sharing of certain genetic and clinical features irrespective of the subtype of SpA and show variable onset, presentation, and progression. Some common manifestations of this group are inflammatory back pain (IBP), peripheral arthritis, enthesitis, anterior uveitis, sacroiliitis, and HLA-B27 positivity [1,3].

SpA patients can also be classified as predominantly peripheral or predominantly axial SpA according to their clinical presentation. There may be some overlap between these two groups [4]. AS is a subgroup of SpA with predominant axial symptoms as a result of sacroiliitis, spondylitis, spondylodiscitis, or enthesitis.

Radiographic sacroiliitis is the classic diagnostic hallmark of AS and therefore included in the modified New York criteria for the diagnosis and classification of AS [5].

Traditionally, patients with SpA may be classified according to European Spondyloarthropathy Study Group (ESSG) criteria or Amor criteria [6,7]. Recently, a new set of criteria has been developed by the Assessment of Spondyloarthritis International Society (ASAS) group to differentiate axial or peripheral SpA [4,8]. It was proposed to consider all SpA patients with predominantly axial involvement as axial SpA irrespective of whether they have definite radiographic sacroiliitis. MRI has evolved as a diagnostic tool in patients with preradiographic axial SpA as it visualizes active inflammation in the sacroiliac joints. Patients with typical features of SpA who do not fulfill the criteria for one of these subgroups have been classified as having undifferentiated spondyloarthritis (uSpA) [4]. They are characterized by episodes of peripheral arthritis and enthesitis, axial symptoms, and

by a lower incidence of HLA-B27 compared with AS patients [9].

The aim of the present study was to describe the clinical, demographic, radiologic, and genetic features of patients with AS and uSpA.

Patients and methods

This study included 225 consecutive patients with SpA (134 uSpA and 91 AS patients) attending the Atatürk Education and Research Hospital Rheumatology Outpatient Clinic. The diagnosis of AS was made according to the modified New York criteria [5]. uSpA patients were diagnosed according to the modified ESSG (with MRI) criteria [6,7]. Patients with associated IBD, psoriasis, a preceding symptomatic infection of the urogenital or the gastrointestinal tract within the 4 weeks before the onset of symptoms, Behçet's disease, or familial Mediterranean fever were excluded. Patients who did not fulfill criteria for AS, ReA, PsA, IBD/SpA, or juvenile SpA were categorized as having uSpA. The study protocol was approved by the local ethics committee and was carried out in accordance with the Helsinki Declaration of 2008. The study was carried out by one investigator and patient charts were evaluated retrospectively. Radiographic evaluation was also performed by one investigator. Patients underwent peripheral and axial joint and entheses assessment, erythrocyte sedimentation rate or C-reactive protein determination, radiographic evaluation of the pelvic region to evaluate the sacroiliac joints, and radiography to evaluate enthesopathy. Sacroiliac MRI was also performed for every patient. Time for evolution of symptoms meant the time from beginning of symptoms. Diagnostic delay meant the time from the beginning of symptoms to the time of diagnosis.

IBP is defined as the presence of at least four of the following five parameters:

- (1) Age at onset less than 40 years;
- (2) Insidious onset;
- (3) Improvement with exercise;
- (4) No improvement with rest;
- (5) Pain at night (with improvement upon getting up) [10].

HLA tissue typing was performed as follows: venous blood was obtained from each patient. The DNA was isolated from samples of blood collected into ACD using a high-quality DNA extraction kit (QIAamp DNA Blood Mini Kits; Qiagen). DNA was resuspended in deionized water and stored at -20°C until its use for

the PCR. HLA-B27 typing was performed by a PCR using sequence-specific primers. The low-resolution HLA-B genotyping was performed using commercial kits (Olerup SSP HLA-B*27; Olerup; Saltsjöbaden, Sweden).

Statistical analysis

Statistical analysis was carried out using SPSS (version 17; SPSS Inc., Chicago, Illinois, USA) statistics program for Windows. All the numerical variables are expressed as mean \pm SD and median (minimum–maximum). The χ^2 -test and Student's *t*-test were used to analyze the differences between groups. Mann–Whitney *U* analysis was used for nonparametric variables to compare differences among groups where necessary. *P* value less than 0.05 was considered significant.

Results

In total, 26 of 91 (28.6%) AS patients were women and 65 (71.4%) were men. One hundred and fifteen of 134 (85.8%) uSpA patients were women and 19 (14.2%) were men. The difference between the sex distribution of the two groups was statistically significant ($P < 0.001$). AS patients were significantly younger than the uSpA patients. Time for evolution of symptoms was 9.85 ± 8.12 years for AS patients and 6.68 ± 5.1 years for uSpA patients ($P = 0.005$). Time for diagnosis was 15.82 ± 20.7 months for AS patients and 5.91 ± 3.63 months for uSpA patients. Diagnostic delay was significantly longer for AS patients than uSpA patients (Table 1).

Family history for rheumatic disease, HLA-B27 positivity, IBP, peripheral joint involvement (as arthritis or arthralgia), enthesopathy, eye involvement, and mean Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) level were significantly different between AS and uSpA patients ($P < 0.001$).

The presenting symptom was back pain in 41.8% of AS and 9.7% of uSpA patients ($P < 0.001$), arthralgia in 15.3% of AS and 49.3% of uSpA patients ($P < 0.001$), both back pain and arthralgia in 31.9% of AS and 38% of uSpA patients ($P < 0.005$), and eye involvement in 11% of AS and 3% of uSpA patients ($P < 0.001$) (Table 2).

A previous history of infection was positive such as diarrhea in 9.9% of AS and 3.7% of uSpA patients ($P = 0.06$), cervicitis/urethritis in 0% of AS and 1.5% of uSpA patients, and cystitis in 2.2% of AS and 8.2% of uSpA patients.

Table 1 Characteristics of patients with ankylosing spondylitis and undifferentiated spondyloarthritis

	AS (n = 91)	uSpA (n = 134)	P value
Female/male	26/65 (28.6/71.4)	115/19 (85.8/14.2)	<0.001
Age (years)	37 (17–66)	46 (17–72)	<0.001
Time of evolution	9.85 ± 0.85	6.67 ± 0.43	<0.05
Disease duration (years)	16 ± 2	6	<0.001
Diagnosis delay (months)	102 ± 88 (83, 8–377)	74 ± 60 (55.5, 0–238)	<0.001
HLA-B27 positive (%)	51.6	14.9	<0.001
Family history (%)	63.7	37.3	<0.001
IBP (%)	98.9	74.6	<0.001
Arthralgia/arthritis (%)	74.7	97	<0.001
Enthesopathy (%)	49.5	70.1	<0.001
Eye involvement (%)	20.9	3.7	<0.001
BASDAI	6.4 ± 1.1	4.8 ± 2.1	<0.001
CRP (mg/l)	21 ± 24 (12, 1–121)	8 ± 12 (3.5, 3–104)	<0.001
ESR (mm/h)	32 ± 24 (30, 2–90)	22 ± 15 (18.5, 2–96)	<0.001
FABER test (%)	81.3	81.3	NS
SI syndrome (%)	68.1	39.6	<0.001

Values are represented as mean ± SD or median (minimum–maximum) or n (%); AS, ankylosing spondylitis; BASDAI, Bath ankylosing spondylitis disease activity index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IBP, inflammatory back pain; SI, sacroiliac; uSpA, undifferentiated spondyloarthritis.

Table 2 First signs/symptoms attributable to the disease

	AS	uSpA	P
IBP	41.8	9.7	<0.001
Arthralgia/arthritis (%)	15.4	49.3	<0.001
IBP and arthralgia (arthritis) (%)	32	38	NS
Eye involvement (%)	11	3	<0.001
Dactylitis (%)	0	0	
Enthesitis (%)	0	0	

AS, ankylosing spondylitis; IBP, inflammatory back pain; uSpA, undifferentiated spondyloarthritis.

Thirty-six percent of patients with AS were using sulfasalazine alone, 23% were using a combination of sulfasalazine and methotrexate, 21% were using anti-tumor necrosis factor- α treatment, and 16% were using NSAIDs alone. Forty-five percent of uSpA patients were using sulfasalazine, 21% were using sulfasalazine and methotrexate combination treatment, and 33% were using other drugs such as NSAIDs, leflunomide, hydroxychloroquine, or colchicine. None of the uSpA patients were using anti-tumor necrosis factor- α treatment.

Discussion

Our study confirms that SpAs are quite prevalent in this country and have some similar findings to AS. In some other studies, it was shown that AS and uSpA have similar BASDAI scores, enthesitis, and uveitis [11,12].

Axial SpAs comprise AS and nonradiographic axial SpA. Recently, it was shown that HLA-B27 positivity, IBP, arthritis, enthesitis, uveitis, and disease activity measures were highly comparable between patients with these two types of diseases, suggesting that they are part of the same disease [13].

Traditionally, patients with SpA may be classified according to Amor *et al.* [7] and the ESSG criteria. Patients with SpA who do not fulfill these diagnostic criteria remain unclassified and comprise the subgroup known as uSpA [6]. uSpA are characterized by axial and/or peripheral joint involvement, enthesitis, and potential extra-articular manifestations [10].

MRI is the most sensitive diagnostic tool to detect early inflammatory changes in sacroiliac joints [14]. It is included in the new ASAS criteria for early diagnosis of axial SpA. We often use MRI for the diagnosis of early axial or peripheral SpA.

In the present study, although IBP was the most common initial symptom in AS patients, arthralgia/arthritis was the most common presenting symptom in uSpA patients. Eye involvement was more common in AS patients as the first presenting symptom. Interestingly, none of the patients had dactylitis or enthesitis as the first manifestation.

The most striking finding of the present study was the predominance of women in the uSpA group. This was in agreement with the study of Roussou and Sultana [15] and Kiltz *et al.* [16]. uSpA patients were significantly older than AS patients. Late onset of disease is more frequent in a subset of patients with SpA than in those with AS and has a more equal distribution by sex. In another study, the male to female ratio was 77–23% in AS and 62.5–37.5% in uSpA [17].

In the present study, the diagnostic delay was 102.46 ± 88.99 (median 83, range 8–377) and 74.23 ± 60.7 (median 55.5, range 0–238) months. In several studies, the diagnostic delay varied between 0

and 11 years [1,9]. The greater diagnostic delay in the AS group was probably related to the predominance of men in this group as male patients were less likely to attend healthcare units for their complaints. Also, most of the patients had been diagnosed previously with lumbar discopathy or fibromyalgia, which may also have caused a diagnostic delay for SpA.

Similar to previous studies [12,18,19], the HLA-B27 positivity was significantly lower in patients with uSpA compared with patients with AS (51.6 vs. 14.9%). In different studies, the frequency of HLA-B27 varies between 64 and 86.7% [20]. The frequency of HLA-B27 was 70.3% in Chinese uSpA patients [21]. In another study, it was 53.6% in uSpA and 78.9% in AS patients [9]. In some other studies, HLA-B27 positivity was found in 65, 39, 60, and 45.3% of the participants of the study [18,20,21]. Interestingly, in our population, HLA-B27 positivity was lower than that in the other populations. Genetic factors other than HLA-B27 and environmental factors may play a role in the development of the disease.

In the present study, the most common extra-articular involvement was uveitis, which was 20.9% for AS and 3.7% for uSpA patients. In several studies, the frequency of uveitis ranges between 7.2 and 20.2% [20].

In the study of Buschiazzo *et al.* [22], a family history was found in 16.8 and 20.9% of AS patients, and 6.1% of uSpA patients had a family history for SpA. In the study of Buschiazzo *et al.* [23], family history was positive in 18% of patients. In the present study, although the HLA-B27 frequency was low, family history was 63.7% for AS and 37.3% for uSpA patients. Besides the genetic predisposition, environmental factors may play a role in the tendency to develop SpA and therefore assessment of family history is important for the diagnosis of SpA.

The frequency of enthesitis was high in both groups (49.5% of axial spondylitis patients and 70.1% of uSpA patients). Peripheral joint involvement and enthesopathy were important characteristic findings in patients with SpA. Increased frequency of enthesopathy in the SpA group shows the need for lateral radiographies that are cheap and easy to perform for the diagnosis of SpA.

The ASAS classification criteria were developed to improve the sensitivity of criteria for early SpA, especially in patients with nonradiographic SpA, who are at risk of developing AS in contrast to patients with predominant peripheral involvement, considered to be at low risk of developing AS. SpA patients may have prominent axial or peripheral symptoms concurrently

and this manifestation may change with time. The classification may change from axial to peripheral and vice versa at different stages of the disease, jeopardizing the consistency of classifications in clinical trials. In the present study, we used the modified New York criteria as ASAS criteria can be used for the diagnosis of axial SpA, but not for the diagnosis of AS as some of the preradiographic axial SpA patients never develop AS.

The advent of MRI accelerates the possibility of early diagnosis of sacroiliitis, and provides the opportunity for the use of new biological treatments. Therefore, we performed sacroiliac MRI for all of our SpA patients.

The limitations of the present study are the lack of follow-up results of the patients after the therapy and its retrospective design.

SpAs are frequent diseases and physicians, especially family practitioners, physiatrists, neurosurgeons, and orthopedists, should be aware of them. Patients previously diagnosed lumbar discopathy or fibromyalgia should be re-evaluated each time for the presence of SpA. Clinical findings and disease activity measures were comparable between the two groups of SpA. Early diagnosis of SpA is important because unnecessary operations for lumbar discopathies can be prevented in this way and early treatment with new biological therapies may yield much better results than applying them in the advanced stages.

Acknowledgements

The authors thank Ferhat Baş for his technical support.

Conflicts of interest

There are no conflicts of interest.

References

- 1 Rojas-Vargas M, Muñoz-Gomariz E, Escudero A, Font P, Zarco P, Almodovar R, *et al.*, Registro Español de Espondiloartritis de la Sociedad Española de Reumatología Working Group. First signs and symptoms of spondyloarthritis — data from an inception cohort with a disease course of two years or less (REGISPONER-Early). *Rheumatology (Oxford)* 2009; 48:404–409.
- 2 Onen F, Akar S, Birlık M, Sari I, Khan MA, Gurler O, *et al.* Prevalence of ankylosing spondylitis and related spondyloarthritis in an urban area of Izmir, Turkey. *J Rheumatol* 2008; 35:305–309.
- 3 Zochling J, Brandt J, Braun J. The current concept of spondyloarthritis with special emphasis on undifferentiated spondyloarthritis. *Rheumatology (Oxford)* 2005; 44:1483–1491.
- 4 Rudwaleit M, van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, *et al.* The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009; 68:777–783.
- 5 Van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984; 27:361–368.
- 6 Dougados M, van der Linden S, Juhlin R, Huitfeldt B, Amor B, Calin A, *et al.* The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum* 1991; 34:1218–1227.

- 7 Amor B, Dougados M, Mijiyawa M. Criteria of the classification of spondylarthropathies. *Rev Rhum Mal Osteoartic* 1990; 57:85–89.
- 8 Rudwaleit M, van der Heijde D, Landewé R, Akkoc N, Brandt J, Chou CT, *et al.* The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis* 2011; 70:25–31.
- 9 Burgos-Vargas R, Casasola-Vargas JC. From retrospective analysis of patients with undifferentiated spondyloarthritis (SpA) to analysis of prospective cohorts and detection of axial and peripheral SpA. *J Rheumatol* 2010; 37:1091–1095.
- 10 Cruzat V, Cuchacovich R, Espinoza LR. Undifferentiated spondyloarthritis: recent clinical and therapeutic advances. *Curr Rheumatol Rep* 2010; 12:311–317.
- 11 Uppal SS, Abraham M, Chowdhury RI, Kumari R, Pathan EM, Al Rashed A. Ankylosing spondylitis and undifferentiated spondyloarthritis in Kuwait: a comparison between Arabs and South Asians. *Clin Rheumatol* 2006; 25:219–224.
- 12 Liao HT, Chen HA, Chen CH, Wang HP, Tsai CY, Chang HN, Chou CT. Undifferentiated spondyloarthropathy in Chinese patients. *Arch Med Res* 2006; 37:384–387.
- 13 Rudwaleit M, Haibel H, Baraliakos X, Listing J, Märker-Hermann E, Zeidler H, *et al.* The early disease stage in axial spondylarthritis: results from the German Spondyloarthritis Inception Cohort. *Arthritis Rheum* 2009; 60:717–727.
- 14 Zochling J, Baraliakos X, Hermann KG, Braun J. Magnetic resonance imaging in ankylosing spondylitis. *Curr Opin Rheumatol* 2007; 19:346–352.
- 15 Roussou E, Sultana S. Early spondyloarthritis in multiracial society: differences between gender, race, and disease subgroups with regard to first symptom at presentation, main problem that the disease is causing to patients, and employment status. *Rheumatol Int* 2012; 32:1597–1604.
- 16 Kiltz U, Baraliakos X, Karakostas P, Igelmann M, Kalthoff L, Klink C, *et al.* Do patients with non-radiographic axial spondylarthritis differ from patients with ankylosing spondylitis? *Arthritis Care Res (Hoboken)* 2012; 64:1415–1422.
- 17 Olivieri I, Salvarani C, Cantini F, Ciancio G, Padula A. Ankylosing spondylitis and undifferentiated spondyloarthropathies: a clinical review and description of a disease subset with older age at onset. *Curr Opin Rheumatol* 2001; 13:280–284.
- 18 Collantes E, Veroz R, Escudero A, Muñoz E, Muñoz MC, Ciscal A, Perez V. Can some cases of 'possible' spondyloarthropathy be classified as 'definite' or 'undifferentiated' spondyloarthropathy? Value of criteria for spondyloarthropathies. Spanish Spondyloarthropathy Study Group. *Joint Bone Spine* 2000; 67:516–520.
- 19 Huerta-Sil G, Casasola-Vargas JC, Londoño JD, Rivas-Ruiz R, Chávez J, Pacheco-Tena C, *et al.* Low grade radiographic sacroiliitis as prognostic factor in patients with undifferentiated spondyloarthritis fulfilling diagnostic criteria for ankylosing spondylitis throughout follow up. *Ann Rheum Dis* 2006; 65:642–646.
- 20 Sampaio-Barros PD. Epidemiology of spondyloarthritis in Brazil. *Am J Med Sci* 2011; 341:287–288.
- 21 Liao Z, Lin Z, Xu M, Hu Z, Li T, Wei Q, *et al.* Clinical features of axial undifferentiated spondyloarthritis (USpA) in China: HLA-B27 is more useful for classification than MRI of the sacroiliac joint. *Scand J Rheumatol* 2011; 40:439–443.
- 22 Valle-Oñate R, Candia L, Romero-Sánchez C, Iglesias-Gamarra A, Caballero-Urbe CV, Santos-Moreno P, *et al.* Epidemiology of spondyloarthritis in Colombia. *Am J Med Sci* 2011; 341:293–294.
- 23 Buschiazzo E, Maldonado-Cocco JA, Arturi P, Citera G, Berman A, Nitsche A, Rillo OL, RESPONDIA Group. Epidemiology of spondyloarthritis in Argentina. *Am J Med Sci* 2011; 341:289–292.