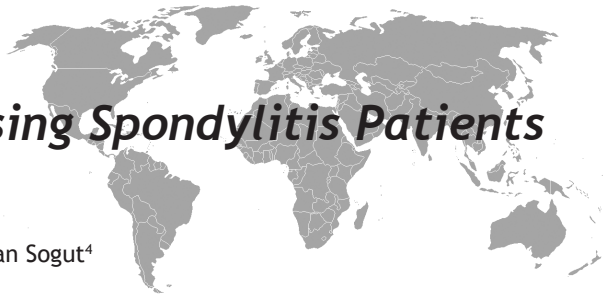

Outcomes of Turkish Ankylosing Spondylitis Patients

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ABSTRACT

*Ankylosing spondylitis (AS) is chronic, progressive, systemic inflammatory rheumatic diseases that lead to serious disability. The objective of this study was to determine the demographic, clinic characteristics and CYP2D6*4 gene mutation profiles of the AS patients in Tokat, Turkey. In this retrospective study, we evaluated 103 patients that were diagnosed and followed up as AS in Tokat, Turkey between 2008-2011. Demographical properties (age, sex, education level, age at diagnosis, disease duration), clinical characteristics (HLA27, peripheral/extraarticular involvoment, chest expansion, enthesopathy, modified schouber) and genetic analysis results (CYP2D6*4 gene mutation frequency) of AS patients were assessed. The mean age of AS patients was 36.80±9.25 years. The mean age of female and male 39.10±7.89, 35.40± 9.79 respectively. The female to male ratio was 1:1.6. Major histocompatibility complex, class I, B 27 (HLAB27) was investigated and the rate of positivity was 73.78 %. There was a statistically significant difference between CYP2D6 gene mutation and peripheral /extraarticular involvement (p<0.05). Determining the clinical characteristics and CYP2D6*4 gene mutations of rheumatologic diseases as AS will provide benefits for early diagnosis, treatment, and disease outcome.*

Key words: *Ankylosing spondylitis, CYP2D6 gene, clinical characteristics*

Türk Ankilozan Spondilit Hastalarının Sonuçları

ÖZET

*Ankilozan Spondilit (AS) kronik, ilerleyici, sistemik, inflamatuvar ve yetersizliğe yol açan romatizmal bir hastalıktır. Bu çalışmanın amacı, Tokat bölgesindeki AS'li hastaların demografik, klinik özelliklerini ve CYP2D6*4 gen mutasyon profilini belirlemektir. Bu çalışmada, Tokat bölgesinde 2008-2011 yılları arasında teşhis ve tedavi edilen 103 AS'li hastanın demografik özellikleri (yaş, cinsiyet, eğitim düzeyi, tanı yaşı, hastalık süresi), klinik özellikleri (HLA27, periferik eklem ve extraartiküler tutulum, göğüs ekspansiyonu, entesopati, modifiye schouber) ve genetik analiz sonuçları (CYP2D6*4 gen mutasyon sıklığı) değerlendirildi. AS'li hastaların yaş ortalaması 36.80±9.25 yıl idi. Kadın ve erkek hastaların ortalama yaşları sırası ile 39.10±7.89, 35.40± 9.79 yıl olarak saptandı. Kadın/erkek oranı 1:1.6 idi. Major histokompatibilite kompleksi, sınıf I, B 27 (HLAB27) incelendi ve pozitiflik oranı 73.78 % olarak belirlendi. CYP2D6 gene mutasyonu ve periferal/extraartiküler tutulum arasında istatistiksel olarak anlamlı farklılık saptandı (p<0.05). AS gibi romatolojik hastalıkların klinik özelliklerini ve CYP2D6*4 gen mutasyonunu belirleme hastalığın erken tanı, tedavi ve sonucu açısından kayda değer yararlar sağlayabilir.*

Anahtar kelimeler: *Ankilozan spondilit, CYP2D6 geni, klinik özellikler*

INTRODUCTION

Ankylosing spondylitis (AS) is a systemic, chronic, progressive inflammatory disease which mostly affects the musculoskeletal system (1). There are a lot of retrospective studies have been designed to predict the prevalence of AS (1,2). In Turkey, the prevalence of AS and related spondyloarthritis have been determined as 0.49% and 1.05%, respectively, and this results are higher than the observed prevalence in other countries (3). Analysis of disease characteristics will inform us about the disease severity and activity in AS patients and could help in selecting candidate patients for biological treatments (1).

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Table 1. Characteristics of the patients with AS

	All patients	Min-Max	Median
n	103		
Average age ±SD (yr)	36.80±9.25	20-60	37
Average duration ±SD (mnt)	69.16±57.604	6-240	48
Average age at diagnosis ±SD (yr)	33.51± 8.56	17-58	34
Modified schober ±SD	4.19±1.233	1-7	4
Chest expansion ±SD	3.782±1.205	1-7	4
Morning stiffness ± (min)	24.56±33.675	0-180	15

CYP2D6 gene influence susceptibility to AS (4). The objective of this study was to determine the demographic, clinic characteristics and CYP2D6*4 gene mutation profiles of the AS patients in Tokat, Turkey.

MATERIALS AND METHODS

Patients

This study included 103 AS patients from the department of Physical Medicine and Rehabilitation, Gazi Osmanpaşa University in Tokat, Turkey. Informed consent was obtained from all participants. Diagnosis of AS was based on the modified New York criteria (5). Disease characteristics, clinical findings and genetics analysis results (CYP2D6 gene) of the patients were investigated.

Statistical Analysis

Analysis of the data was performed using the computer software SPSS 15.0 (SPSS, Chicago,IL, USA) and OpenEpi Info software package programme (6). Continuous data were given as mean ± SD (standard deviation) and (min-max). The categorical variables were evaluated by chi-square or Fisher's exact test, which where applicable. P value smaller than 0.05 (two-tailed) was regarded as statistically significant.

RESULTS

A total of 103 [39 (37.86%) female; 64(61.14%) 64 male] AS patients were evaluated in this study and the female to male ratio was 1:1.6. The mean age of the patients was 36.80±9.25 (20–60) years. The ages and characteristics of disease are given in Table 1. Sex-based disease characteristics of patients with AS are shown in Table 2. Male ratio was higher than women but average age mean was higher in women. HLA-B27 positivity was 53.4 % in our study. Of the AS patients 20.38% have positive family history, 84.86% patients have peripheral involvement 26.22% have extraarticular involvement. Enthesopathy was found in 89 (86.4%) of our patients. In radiographic evaluation, 99.03% of patients had sacroiliitis. HLAB27 positivity, Enthesopathy, peripheral/extrarticular involvement, sacroiliitis ratio was higher in the male group (Table 3). Most of the patients (41.7%) were taking NSAID+ Sulphasalazine theraphy. 26.2%s of patient were taking NSAID and 19.4% were taking Anti-tnf + NSAID theraphy respectively (Table 4). Sociodemographic characteristics of AS patients were seen in Table 5. Educational level of patients was low and smoking ratio was high (82.52%). When we examine clinical characteristics according to exercise habit and smoking status of AS patients, there was a statistically significant difference between enthesopathy and exercise habit ($p<0.05$). CYP2D6*4 gene mutation disribution of AS patients are seen in Table 6. When we examine

Table 2. Sex-based disease characteristics of patients with AS

	Females (mean±SD)(max-min)	Males (mean±SD)(max-min)
n (%)	39 (37.86%)	64 (61.14%)
Average age (yr)	39.10±7.89 (20-55)	35.40±9.79 (20-60)
Disease duration (mnt)	46.00±35.90 (6-180)	83.27±63.7 (6-240)
Age at diagnosis (yr)	35.51±±7.17 (19-50)	32.29±9.14 (17-58)
Modified Schober	4.33±1.143 (2.5-7)	4.11±1.286 (1-6.5)
Chest expansion	3.74±0.985 (1.5-6)	3.850±1.329 (1-7)
Morning stiffness (min)	26.15±36.535 (1-120)	23.595± (0-180)

***Table 3**. Clinical findings and peripheral involvement of the patients with AS*

Clinical characteristcs	*Al patients (n:103) (%)*	*Females (n:39) (%)*	*Males (n:64)(%)*
HLAB-27 positive	*76 (73.78)*	*31 (30.09)*	*45 (43.69)*
Positive family history	*21 (20.38)*	*9 (8.7)*	*12 (11.6)*
Enthesopathy	*89 (86.4)*	*30 (29.1)*	*59 (57.3)*
Peripheral involvement	*87 (84.46)*	*25 (24.27)*	*62 (60.19)*
Spinal	*55 (53.4)*	*18 (17.5)*	*37 (35.9)*
Cervical	*32 (31.06)*	*7(6.8)*	*25 (24.2)*
Extraarticular involvement	*27(26.22)*	*8 (7.8)*	*19 (18.43)*
Lung	*3 (2.9)*	*-*	*3 (2.9)*
Cardiac	*13 (12.62)*	*4 (3.9)*	*9 (8.73)*
Ocular	*11 (10.7)*	*4 (3.9)*	*7 (6.8)*
Sacroiliitis	*102 (99.03)*	*38 (36.90)*	*64 (62.15)*
unilateral	*14 (13.6)*	*6 (5.8)*	*8 (7.7)*
bilateral	*88 (85.4)*	*32 (31.06)*	*56 (54.3)*

CYP2D6*4 genotype frequencies according to the clinical characteristics in AS patients we found that peripheral /extraarticular involvement was higher in the CYP2D6*4 gene mutation carrier group than non-carrier group ($p<0.05$).

DISCUSSION

Ankylosing spondylitis (AS) is a chronic inflammatory disease of the spine with unknown etiology (7). In the western world the prevalence and incidence of AS are 0.2% and 6/10.000, respectively. In Germany the prevalence is 0.55% and similarly in Turkey the prevelance of AS is 0.49% (7). The strongest known contributing factor for AS, the major histocompatibility complex (MHC) class I molecule human leukocyte antigen (HLA)-B27, is known since 1973 [8]. HLA-B27 positivity was 73.78 % in our study. Similarly in another study conducted by Bodur et al. in Turkey HLA-27 positivity was 73.7% (8). In Caucasians and Chinese population this ratio was >90%. It isalso known that only about 5% of HLA-B27 positive individuals develop AS (8). AS usually affects the younger age group and males. Accordance with this conclusion female to male ratio of the present study was found 1:1.6 and the mean age of the patients was 36.80±9.25 (20–60) years. Similarly Bodur et al. reported that female to male ratio1:2.5 and mean age of the patients was 38.1±10.6 (8). Differently Çağlar et al., reported that male to female ratio 3,4: 1 and means of age 37.1±912 (2). In Asian countries male to female ratio has been reported (7.2:1 and 9.2:1) which is higher than other countries (9,10). In this study 84.46% patients have peripheral involvement, 126.22% patients have extraarticular involvement. The most common was spinal involvement with 53.4%. The rate of peripheral arthritis was reported as 47% for Middle East Arab 50% for South Asian, and 60% for Korean patients (8,9). In radiographic evaluation, 99.03% of patients had sacroiliitis and en-

***Table 4**. Drug use of patients with AS*

Drug	*n (%)*
NSAID + Sulphasalazine	*43(41.7)*
NSAID	*27(26.2)*
Anti-tnf + NSAID	*20(19.4)*
Sulphasalazine + Kolsin	*4(3.88)*
Sulphasalazine	*2(1.94)*
Anti-tnf + Methotreksate	*2(1.9)*
Anti-tnf + Sulphasalazine	*2(1.9)*
Sulphasalazine + Methotreksate	*1(0.95)*
NSAID + Methotreksate	*1(0.95)*
Azathioprine	*1(0.9)*
Total	*103(100)*

***Table 5**. Sociodemographic data and pain profile of patientys with AS*

Sociodemographic characteristics		*Patient (n)(%)*
Education level	*primary/middle school*	*58 (56.3)*
	high School	*31 (30.1)*
	university	*14 (13.6)*
Pain	*morning*	*59 (57.2)*
	walking	*14 (13.6)*
	sitting	*9 (8.7)*
	constantly	*21 (20.4)*
Egzersize	*regularly*	*18(17.42)*
	irregular	*57(55.33)*
	non	*28 (27.18)*
Smoking	*smoker*	*85 (82.52)*
	non-smoker	*18 (17.47)*
Total		*103(100)*

***Table 6**. Clinical characteristics distribution according to exercise habit and smoking.*

Clinical characteristics		Exercise habit n (%)		p value	Smoking n (%)		p value
		Yes	No		Yes	No	
Peripheral/extraarticular	yes	25 (24.27)	13(12.62)		11(10.67)	52(50.48)	
	no	50 (48.54)	5(14.56)	>0.05	7 (6.79)	31(30.09)	>0.05
Enthesopathy	yes	70 (67.96)	19 (18.44)		16 (15.53)	73 (70.87)	
	no	5 (4.85)	9 (8.73)	0.002	2 (1.94)	12 (11.65)	>0.05
Sacroilit	yes	74 (71.84)	28 (27.18)		18 (17.47)	84(81.55)	
	no	1(0.97)	0	>0.05	0	1(0.97)	>0.05

thesopathy was found was found in 89 (86.4%) of our patients. These findings similar to the literature (2,8). When we investigated the therapy of AS patients most of the patients (41.7%) were taking NSAID+ Sulphasalazine theraphy, 26.2% of patient were taking NSAID and 19.4% were taking Anti-tnf + NSAID theraphy respectively in the present study. NSAIDs are widely used to ameliorate spinal pain in AS (11,12). Oniankitan et al. reported that 70% of patients used NSAIDs and 71% DMARD (SSZ and/or MTX) (13). NSAIDs are also widely used to ameliorate spinal pain in AS and TNF blockers seem to have no influence on new bone formation in AS (9,11,12). Sulfasalazine has shown mild to moderate effects on disease-related peripheral symptoms in AS (14). While methotrexate (MTX) is useful in RA, its role in AS is unclear at best. There is little data supporting the use of MTX in patients with AS. The quality of life of patients with AS is decreased in comparison to the normal population (15). Physiotherapy and group exercises are recommended to AS patients. Several studies in AS showed that supervised individual exercises and physical therapy in groups led to significantly better outcomes compared to patients who performed only home exercises without supervision or no physiotherapy at all (8). When we examine clinical characteristics according to exercise habit and smoking status of AS patients, there was a statistically significant difference between enthesopathy and exercise habit ($p<0.05$). According to our result exercise increased enthesopathy risk, so that in the presence of enthesopathy resting should be offered. Based on large family and genome-wide association studies, the susceptibility to AS has been estimated to be 80–90% genetically determined (16). In this study 20.38% of the patients have positive family history. The average risk of developing AS in a first-degree relative of AS patients is about 8%, but only <1% in second-degree relatives. The risk in HLA–B27 positive first-degree relatives is about 12%, but <1% in HLA–B27-negative relatives (8,17). CYP2D6 gene influence susceptibility to AS (4). Brown et al reported that weak linkage demonstrated between CYP2D6 and AS (17). In this study in 53 patients CYP2D6*4 gene mutation frequency of AS patients were assessed. And when we examine CYP2D6*4 genotype frequencies according to the clinical characteristics in AS patients we found that peripheral /extraarticular involvement was higher in the CYP2D6*4 gene mutation carrier group than non-carrier group ($p<0.05$). Based on this finding we may say that CYP2D6*4 gene mutation may influence peripheral /extraarticular involvement in Turkish AS patients. However a study conducted in a different Turkish population showed no significant association between CYP2D6*4 allele and AS (4). Most recently, two new genetic loci have been shown to be associated with AS besides HLA-B27.2: the IL23 R(eceptor), which is involved in the Th(elper cell) 17-pathway of immune responses, and the ARTS-1 or ERAP-1, an enzyme which is relevant for the processing of peptides in the cytoplasm (8,18).

AS related epidemiologic studies have been designed to predict the prevalence. In this study we described the prevalence and clinical characteristics of AS patients in a Turkish population who live in Tokat province. Outcomes of the investigations will probably result in more accurate information for AS.

***Table 7**. Distribution of CYP2D6 gene mutation*

CYP2D6*4	n (%)
Negative (wild type)	37(69.8)
Heterozygote positive	15(28.3)
Homozygote positive	1(1.88)
Total	53(100)

Table 8. *CYP2D6 genotype frequencies according to the clinical characteristics in AS patients*

Clinical characteristics		Homozygote wild type	CYP2D6*4 Heterozygote	Homozygote CYP2D6 mutated	p value
Peripheral/ extraarticular	yes	17(32)	14(26.4)	0	
	no	20(37.7)	1(1.88)	1(1.88)	<0.05
Sacroilit	yes	36(67.92)	15(28.30)	1(1.88)	>0.05
	no	1(1.88)	0	0	
Enthesopathy	yes	30(56.60)	12(22.64)	1(1.88)	>0.05
	no	7(13.20)	3(5.66)	0	

REFERENCES

1. Bodur H, Ataman Ş, Akbulut L, et al. Characteristics and medical management of patients with rheumatoid arthritis and ankylosing spondylitis. Clin Rheumatol 2008; 27:1119-25.
2. Çağlar NS, Burnaz O, Akın T, et al. Demographic and clinical properties and medical treatments of patients followed as ankylosing spondylitis. Istanbul Med J 2011;12:19-24.
3. Onen F, Akar S, Birlik M, et al. Prevalence of ankylosing spondylitis and related spondyloarthritides in an urban area of Izmir, Turkey. J Rheumatol 2008;35:305-9.
4. Erden G, Acar FS, Inal EE, et al. Frequency of mutated allele CYP2D6*4 in the Turkish ankylosing spondylitis patients and healthy controls. Rheumatol Int 2009;29:1431-34.
5. Van der Linden S, Vonder Heide D, Braun J. Ankylosing spondylitis. In: Harris ED, editor. Kelley's textbook of rheumatology 2006; 7th ed. p.1125-38.
6. Dean AG, Sullivan KM, Soe MM. OpenEpi. "Open Source Epidemiologic Statistics for Public Health," Version 2.3.1. www.OpenEpi.com, updated 2010/19/09, accessed 2011/02/21.
7. Bodur H, Ataman S, Rezvani A, et al. Quality of life and related variables in patients with ankylosing spondylitis Qual Life Res 2011;20:543-9.
8. Baraliakos X, Braun J. Spondyloarthritides Best Practice & Research Clinical Rheumatology 2011;25:825-42.
9. Uppal SS, Abraham M, Chowdhury RI et al. Ankylosing spondylitis and undifferentiated spondyloarthritis in Kuwait: a comparison between Arabs and South Asians. Clin Rheumatol 2006;25:219-24.
10. Rudwaleit M, van der Heijde D, Khan MA, Braun J, Sieper J. How to diagnose axial spondyloarthritis early. Ann Rheum Dis 2004; 63:535-43.
11. Zink A, Listing J, Niewerth M, et al. The national database of the German Collaborative Arthritis Centres: II. Treatment of patients with rheumatoid arthritis. Ann Rheum Dis 2001; 60:207-13.
12. Baek HJ, Shin KC, Lee YJ et al. Clinical features of adult-onset ankylosing spondylitis in Korean patients: patients with peripheral joint disease (PJD) have less severe spinal disease course than those without PJD. Rheumatology 2004;43:1526-31.
13. Oniankitan O, Ranaivo N, Carton L et al. Poorly and well controlled spondyloarthropathies: a comparison of 2 groups of patients. J Rheumatol 2005;32:77-9.
14. Braun J, Zochling J, Baraliakos X, et al. Efficacy of sulfasalazine in patients with inflammatory back pain due to undifferentiated spondyloarthritis and early ankylosing spondylitis: a multicentre randomised controlled trial. Ann Rheum Dis 2006; 65:1147-53.
15. Ward MM. Health-related quality of life in ankylosing spondylitis: a survey of 175 patients. Arthritis Care Res 1999;12:247-55.
16. Laval SH, Timms A, Edwards S, et al. Whole-genome screening in ankylosing spondylitis: evidence of non-MHC genetic-susceptibility loci. Am J Human Gen 2001;68:918-26.
17. Brown MA, Laval SH, Brophy S, Calin A. Recurrence risk modelling of the genetic susceptibility to ankylosing spondylitis. Annals of the Rheumatic Diseases 2000;59:883-6.
18. Wu W, Ding Y, Chen Y, et al. Susceptibility to ankylosing spondylitis: evidence for the role of ERAP1, TGFb1 and TLR9 gene polymorphisms. Rheumatol Int 2012;32:2517-21.