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ORIGINAL ARTICLES

A single center experience: physician related diagnostic delay and demographic and clinical differences between patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis

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Background. A large number of comparative studies have been conducted for ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA), including disease burden, treatment modalities and patient characteristics. The aim of this study was to compare physician related diagnostic delay time between patients with AS and nr-axSpA.

Methods. In our retrospective study we included 266 patients with axSpA. Patients were classified into two subgroups, AS and nr-axSpA. The time from back pain onset until diagnosis of axSpA was defined as the diagnostic delay. The first specialist referred to and the first diagnosis for each patient was noted in detail. Patient characteristics, clinical manifestations and laboratory and imaging results at diagnosis were also compared between subgroups.

Results. The diagnostic delay time was significantly longer for AS patients [6 ± 8.14 years vs 1.62 ± 2.54 years]. 40.9% of all patients were initially consulted by specialists in physical therapy and rehabilitation, followed by 29.7% consulted by a neurosurgeon and 19.9% by a rheumatologist. The most common initial diagnosis was fibromyalgia, 52.6% (140), followed by ankylosing spondylitis, 28.9% (77), and lumbar disc hernia, 12.7% (34).

Conclusion. The vast majority of patients were initially evaluated by healthcare providers other than rheumatologists and mostly diagnosed with fibromyalgia. Efforts to increase awareness and to educate first healthcare providers may shorten the diagnostic delay time.

Key words: ankylosing spondylitis, non-radiographic axial spondyloarthritis, axial spondyloarthritis, fibromyalgia, differential diagnosis.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a common chronic inflammatory rheumatologic disease. From the results of numerous community-based studies, its prevalence is approximately 1% of the population [1]. Patients with axSpA are identified as ankylosing spondylitis (AS) or non-radiographic axial spondyloarthritis (nr-axSpA), distinguished by the presence or absence of definitive sacroiliitis on plain radiographs [2]. 5–10% of nr-axSpA patients have been shown to develop AS within 2 years, and 20% of them within 5 years [3]. It is also well known that the progression occurs more frequently in male patients with active sacroiliitis, positive HLA B-27 and high c-reactive protein (CRP) values at diagnosis [4].

Delayed diagnosis and inadequate treatment lead to structural damage, irreversible loss of spinal mobility and poor quality of life in patients with axSpA [5]. Currently, it is thought that AS and nr-axSpA are two different clinical entities in the same spectrum, only differing in terms of chronicity [6]. Therefore, for early diagnosis and timely treatment, it is very important to know the similarities and differences between these two clinical entities.

Recently, many studies have compared patients with AS and nr-axSpA in terms of patient characteristics, disease burden, activity criteria and treatment modalities. The aim of this study was to compare diagnostic delay time, physician related factors (specialists consulted initially and first diagnoses) in addition to all of the above parameters between patients with AS or nr-axSpA.

MATERIAL AND METHODS

Patient selection and definition of axial spondyloarthritis

We evaluated retrospectively the medical records of 360 patients in total between

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December 2019 and January 2020. Overall, 94 of the patients were excluded due to insufficient data and irregular follow-up and 266 patients diagnosed with axSpA between January 1999 and November 2019 were included. All of them were diagnosed with axSpA in our tertiary single center and followed up regularly up to the present in the rheumatology department of internal medicine at Pamukkale University, Denizli. Patients that were diagnosed with axSpA before coming to our center were excluded.

All of the patients fulfilled the 2009 axspa classification criteria of the assessment of spondylo arthritis international society (asas) [7]. all of them had inflammatory back pain initially. sij x-rays were present for all axspa cases. patients with axspa were classified into two subgroups as as or nr-axspa, distinguished by the presence or absence of definitive sacroiliitis and structural damage on the baseline plain radiographs. all of the as cases were diagnosed based upon the modified new york criteria regardless of the presence of hla b-27 [8]. patients with nr-axspa that had no definitive sij changes on plain x-rays underwent mri imaging. only two patients in the nr-axspa group were diagnosed without imaging with hla b-27 positivity. all of the pelvic x-ray and mri scans of the sacroiliac joints were evaluated by the same experienced rheumatologist, who was blinded to the laboratory results and clinical presentations. hip involvement of patients was noted as current or ever by the same experienced rheumatologist. also, mri findings of sacroiliac joints (sijs) were grouped as subchondral bone marrow edema and/or degenerative fatty changes. an additional consultant radiologist was not invited into this study. recent studies have shown that rheumatologists have similar mri interpretations of si joints in spa patients as expert radiologists without any interobserver variation [9].

Definition of disease duration and delay of diagnosis

The first specialist who evaluated the patient and the first diagnosis for each patient before the correct diagnosis were noted. The information notes containing detailed anamnesis and physical examination for each patient were examined in detail. The time from diagnosis to the present was defined as the disease duration. The time from back pain onset until diagnosis of axSpA was defined as the diagnostic delay.

Outcome measures

Patient characteristics (gender, age, disease duration, diagnostic delay, specialists initially referred to and first diagnosis), clinical manifestations, laboratory results [c-reactive protein (CRP), erythrocyte sedimentation rate (ESR), specified as mm/hour and mg/dl, respectively] and imaging results [X-ray, magnetic resonance imaging (MRI)], Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores at diagnosis and treatment modalities were analyzed retrospectively and compared between the two subgroups of AS and nr-axSpA.

All of the patients presented with inflammatory back pain (IBP) initially. Other extra-articular manifestations including uveitis and inflammatory bowel disease, or presence or absence of peripheral arthritis at diagnosis were noted in detail. In the follow-up, information on medication use and drugs were collected from prescriptions in the medical charts. Human Leukocyte Antigen B-27 (HLA B-27) status was noted as positive, negative or not available.

Ethics approval and consent to participate

Local ethical committee approval was obtained from the Ethics Committee of Pamukkale University Faculty of Medicine with the decision dated 15/10/2019 and numbered 15. Written informed consent was not obtained for each patient due to the retrospective nature of the current study.

Statistical analysis

The medical records of patients were obtained using the Probel data system. Analyses of the study were performed with SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version25.0, Armonk, NY: IBM Corp.) and statistical significance was determined as p:0.05. In the study, the suitability of continuous variables to normal distribution was examined by Shapiro-Wilk and Kolmogorov Smirnov Tests. Continuous variables were expressed as mean ± standard deviation and median (interquartile range – IQR), and categorical variables were expressed as number and percent. For independent group comparisons, Mann-Whitney U test was used since parametric test assumptions were not provided. Differences between categorical variables were evaluated using chi-square test.

RESULTS

Overall 266 axSpA patients (60% male) were classified into two subgroups, including 213 (80.1%) patients with AS and 53 (19.9%) patients with nr-axSpA. 143 (67.1%) patients in the AS group and 18 (33.9%) patients in the nr-axSpA group were male [p:0.0001], Table 1. The mean age of patients was 44 (23-77) in the AS group and 37 (18-58) in the nr-axSpA group. In patients with AS compared to nr-axSpA, longer disease duration [10.55 ± 9.68; 3.61 ± 3.67; p:0.0001] was also seen (Table 1). At diagnosis, higher ESR values [29.63 ± 16.44 mm/hour; 23.17 ± 12.59 mm/hour; p:0.011], higher CRP values [1.34 ± 1.57 mg/dl; 0.66 ± 0.67 mg/dl; p:0.004] and higher BASDAI scores [4.49 ± 2.52; 3.08 ± 1.4; p:0.002] were seen in the AS group compared to the nr-axSpA group.

Table 1

Comparison of different parameters between AS and nr-axSpA subgroups

	All patients	AS	nr-axSpA	pvalue
Gender (male) n (%)	161 (60.5%)	143 (67.1%)	18 (33.9%)	p:0.0001*
Disease duration (median ± Standard deviation)	7.08 ± 6.67	10.55 ± 9,68	3.61 ± 3.67	p:0.0001*
Diagnostic delay (median ± Standard deviation)	3.81 ± 5.34	6 ± 8.14	1.62 ± 2.54	p:0.0001*
Number of specialists [mean (min - max)]	2 (1–4)	2 (1 – 4)	1 (1 – 4)	p:0.105
Current peripheral arthritis n (%)	41 (15.4%)	34 (15.9%)	7 (13.2%)	p:0.619
Current uveitis n (%)	17 (6.3%)	17 (7.9%)	0 (0%)	p:0.028*
Current inflammatory bowel disease n(%)	12 (4.5%)	11 (5.1%)	1 (1.8%)	p:0.344
HLA B-27 positive and negative, respectively n (%)	85 (31.9%), 110 (41.3%)	72 (33.8%), 77 (36.1%)	13 (24.5%), 33 (62.2%)	p:0.002*
MRI (subchondral bone marrow edema) n (%)	71 (26.6%)	36 (16.9%)	35 (66%)	p: 0.0001*
Current hip involvement n (%)	28 (10.5%)	28 (13.2%)	0(0%)	p:0.005*
BASDAI (median ± Standard deviation)	3.78 ± 1.96	4.49 ± 2.52	3.08 ± 1.4	p:0.002*
Treatment modalities n (%)				
NSAIDs DMARDs Biologics	46 (17.2%) 44 (16.5%) 176 (66.1%)	22 (10.3%) 30 (14%) 161 (75.5%)	24 (45.2%) 14 (26.4%) 15 (28.3%)	p:0.0001*
First admission outpatient clinics n (%)				
Physical therapy rehabilitation Neurosurgery Rheumatology Orthopedics Others	109(40.9%) 79 (29.7%) 53 (19.9%) 10 (3.7%) 15 (5.5%)	81 (38%) 64 (30%) 44 (20.6%) 9 (4.2%) 15 (7%)	28 (52.8%) 15 (28%) 9 (16.9%) 1 (1.8%) 0(0%)	p:0.079
First diagnosis n (%)				
Fibromyalgia Lumbar disc hernia AxSpA Nonspecific back pain Osteoarthritis	140 (52.6%) 34 (12.7%) 77 (28.9%) 12 (4.5%) 3 (1.1%)	130 (61%) 29 (13.6%) 45 (21.1%) 7 (3.3%) 2 (0.9%)	10 (18.8%) 5 (9.4%) 32 (60.3%) 5 (9.4) 1 (1.8%)	p:0.005*

AS: ankylosing spondylitis, nr-axSpA: non-radiographic axial spondyloarthritis, HLA B-27: human leukocyte antigen B-27, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, NSAIDs: nonsteroidal anti-inflammatory drugs, DMARDs: disease-modifying antirheumatic drugs, AxSpA: axial spondyloarthritis, p*: statistically significant

Until the correct diagnosis, the mean number of specialists who evaluated the patients was 2 and 1 in AS and nr-axSpA groups, respectively [p:0.105]. Among 266 patients with axSpA, the mean diagnostic delay time was significantly longer in AS patients compared with nr-axSpA patients, respectively [6 ± 8.14(year); 1.62 ± 2.54 (year); p:0.0001].

Patients were first evaluated by a physical therapy and rehabilitation physician, 109 (40.9%), by a surgeon, 89 (33.4%) (79 neurosurgery, 10 orthopedic), rheumatologist 53 (19.9%), or others 15 (5.6%) (13 internal medicine physicians, 2 general practitioners). Physicians of physical therapy and rehabilitation were more frequently seen by nr-axSpA patients than AS patients [52.8% (28), 38% (81), p:0.079]. The most common initial diagnosis was fibromyalgia, 140 (52.6%), followed by axSpA, 77 (28.9%), lumbar disc hernia, 34 (12.7%), non-specific low back pain, 12 (4.5%) or osteoarthritis, 3 (1.1%). According to the first diagnosis, the accuracy of axSpA diagnosis was more prominent in the nr-axSpA group than the AS group (60.3% vs 21.1%, p:0.005). In contrast, a first diagnosis of fibromyalgia was more frequent in the AS group than the nr-axSpA group (61.0% vs 18.8%, p:0.005). Accuracy of axSpA diagnosis was higher for rheumatologists than physicians of physical therapy and rehabilitation and surgeons, 83.0%, 23.8%, 6.7%, respectively (Table 2).

Treatment modalities were statistically different between patient groups (p:0.0001). The vast majority of patients were on treatments with biologic agents (75.5%) in the AS group whereas it was only 28.3% in the nr-axSpA group. Nearly half of patients with nr-axSpA were treated with only NSAIDs.

Table 2

The first diagnoses and physicians among all of the patients (n)

		Department of physicians			
		Physical Therapy Rehabilitation (n=109)	Surgeons (n=89)	Rheumatology (n=53)	Others (n=15)
First Diagnosis (n=266)	Fibromyalgia (n=140, 52.6%)	83 (76.2%)	42 (47.1%)	1 (1.8%)	14 (93.3%)
	AxSpA (n=77, 28.9%)	26 (23.8%)	6 (6.7%)	44 (83.0%)	1 (6.7%)
	Lumbar Disc Herniation (n=34, 12.8%)	0	33 (37%)	1 (1.8%)	
	Nonspecific (n=12, 4.5%)	0	6 (6.7%)	6 (11.3%)	
	Osteoarthritis (n=3, 1.1%)	0	2 (2.2%)	1 (1.8%)	

DISCUSSION

In our study we found that the vast majority of patients were first evaluated by specialists of physical therapy and rehabilitation (FTR) and surgeons before specialists of rheumatology, and the most common initial diagnosis was fibromyalgia, accounting for 52.6% of all patients. Deodlar A. et al. has stated that only 37% of patients with AS are diagnosed by rheumatologists, the remaining 63% being diagnosed by primary care (26%), physical therapy (7%), orthopedic surgery (4%) and pain clinics (4%), and the estimated diagnostic delay for axSpA is 14 years [10]. Vedat G et al. stated that the diagnostic delay was 8.1 years among 393 patients with AS. Lumbar disc hernia (LDH) was the most reported initial diagnosis for about 33% of patients, and prior diagnosis of LDH was a predictive factor for diagnostic delay [11]. In a community wide epidemiologic study it was shown that many patients with axSpA were referred to specialties other than rheumatologists, such as orthopedics, spine surgeons and rehabilitation medicine via primary care doctors [12]. As in the above mentioned studies, physician related factors (referral delay) and incorrect diagnoses were additional important reasons for the diagnostic delay in our study, correlating with previous literature.

In addition, lack of validated diagnostic criteria, reliable biomarkers and limitations on physical examination of the back and SIJs lead to late recognition of axSpA. Although chronic back pain in commonly seen, the entry criteria is inflammatory back pain for axSpA. About 13% of adults suffer from chronic back pain in the general population, and axSpA accounts for only 5% of cases [13]. Healthcare providers other than rheumatologists may not be aware of the prevalence and importance of axSpA and may be unfamiliar with presentation of the disease as inflammatory back pain.

Although the majority of patients in both groups were evaluated by FTR specialists initially, more than half of the patients in the nr-axSpA group were diagnosed with axSpA at first admission because MRI scans were performed for the vast majority of patients (96.2%) in this group. We believe that the presence of active sacroiliitis on MRI contributes greatly to the early diagnosis and abbreviates the diagnostic delay time in patients presenting with appropriate clinical symptoms. But it should be kept in mind that subchondral bone marrow edema on MRI is not specific evidence for axSpAsince it can be seen in 23% of those with mechanical low back pain and in 7% of healthy volunteers [14]. Mild inflammatory changes may also be seen in healthy athletes. Today, although MRI is the most sensitive imaging determiner, another important point is that positive MRI findings alone can result in over-diagnosis of axSpA [15]. Because of the high cost, sacroiliitis on MRI should not be an entry screening method. Especially for appropriately selected patients presenting with inflammatory back pain and without findings of sacroilitis on plain x-ray as in our study, many of them may be diagnosed at an early, non-radiographic state of disease using combined MRI and ASAS criteria [16]. Another point is that performing MRI is a relatively new imaging method for diagnosis of axSpA. Disease duration was higher in AS patients in our study. Limited possibilities of MRI examinations in the early 2000s may have contributed to diagnostic delay in AS patients.

In a cohort study involving 755 axSpA patients, the AS group showed male dominance, higher mean age, higher inflammatory markers and more frequent radiographic damage compared to nr-axSpA [17]. Also Clementina Medina et al. reported longer disease duration, longer time to diagnosis, higher CRP levels and higher BASDAI values to be more common in AS patients compared to nr-axSpA, and each poses a risk of structural damage [18]. All of the above findings correlated with the findings of our study. Extra-articular manifestations occur in 25–35% of axSpA patients [1]. In our study there was no significant difference between the two subgroups in terms of the frequency of inflammatory bowel disease, but the frequency of uveitis [7.9%, 0%; p:0.028] was significantly higher in patients with AS than nr-axSpA patients. This condition may be related to the longer disease duration. Hip involvement has been demonstrated in 25-35% of patients with AS, associated with greater functional limitation and worse prognosis, but has not been studied in nr-axSpA patients. It has been reported that it is more common in patients with early onset AS, and with axial and entheseal disease [19]. In our study, hip involvement was detected in 13.2% of patients with AS, but was not detected in the nr-axSpA group [13.2%, 0%; p:0.005]. Positive HLA B-27 and high CRP are the most commonly used laboratory biomarkers for axSpA. HLA B-27 positivity in nr-axSpA and AS groups was 77% and 78%, respectively [7]. Imke Redeker et al. stated that among 1677 patients with axSpA, HLA B-27 negativity was a risk factor for longer diagnostic delay time [20]. In our study HLA B-27 was not studied in one third of AS patients. Also, this condition may be one of the causative factors for diagnostic delay. It was stated that both AS and nr-axSpA had comparable burden of disease and treatment modalities [18]. But the result drawn from our study is that use of anti-tumor necrosis factor (anti-TNF) agents was significantly higher in patients with AS, whereas NSAIDs were sufficient for approximately half of patients in the nr-axSpA group.

Various referral strategies have been developed for early diagnosis. The vast majority of them include one or more typical spondyloarthritis features in addition to inflammatory back pain for >3 months and age of onset <45 as entry criteria. Using these candidate parameters, about 35–45% of patients were diagnosed early with axSpA [21]. In a PROSpA study, 751 patients had inflammatory back pain (IBP) beginning at an age of <45 years. The presence of 1 of 3 criteria, including HLA B-27 positivity, current IBP and MRI evidence, is effective for early diagnosis in 46% of patients with axSpA [22]. A combination of AWARE criteria indicative for IBP and positive imaging or HLA B-27 positivity also benefits in the early detection

of patients with axSpA [23]. ASAS and Brandt I strategies are the most sensitive (98%) but have low specificity (18% and 11%, respectively). According to Brandt I strategies, patients are referred to a rheumatologist if HLA B-27 positivity and/or IBP is present [24]. The conclusion drawn from the above studies is that inflammatory back pain is the most important entry criteria for referral. Although all of the patients in our study had inflammatory back pain initially, more than half of them were considered to have fibromyalgia. So the differences between inflammatory and mechanical back pain should be precisely explained to health care professionals who first meet patients. HLA B-27 positivity and positive MR imaging, as in our study, and extra-articular clinical manifestations may have a contributory effect in referring patients to appropriate specialists. Patients with acute anterior uveitis, inflammatory bowel disease and psoriasis may be target populations [6]. Therefore, specialists including ophthalmologists, gastroenterologists and dermatologists who manage extra-articular manifestations of axSpA may be good sources for patient referral.

Our study had a few limitations that should be noted. One of the major limitations was that it was a retrospective study. The other limitation of our study was related to patient groups. The sample size in the nr-axSpA group was small and the patient groups were non-homogeneous, especially for HLA B-27. Another point is that although the same rheumatologist analyzed all files of each patient including anamnesis, physical examination notes, imaging and laboratory results, all of the patients initially were evaluated by different rheumatologists at their outpatient visits. This study was also a single center experience. The patient images were evaluated by the same experienced rheumatologist. We think that it is not a major problem in clinical practice since rheumatologists are highly experienced in interpretation of radiological images of SIJs.

Today it is well known that early diagnosis and timely treatment improve symptoms and function among young adults with axSpA. As a result of diagnostic delay, patients more commonly experience functional limitations and disability. We must work to increase awareness among non-rheumatologist healthcare providers. Therefore, education of referring providers is very important. Also, validated referral strategies are necessary for selected patients in our country.

CONCLUSION

The vast majority of patients were initially evaluated by healthcare providers other than rheumatologists and mostly diagnosed with fibromyalgia. Efforts to increase awareness and to educate first healthcare providers may shorten the diagnostic delay time.

Introducere. *Un număr crescut de studii au fost realizate la pacienții cu spondilită anchilozantă (AS) și spondilartropatie axială nonradiologică (nr-axSpA). Scopul studiului a fost de a compara întârzierea diagnostică la pacienții cu As comparativ cu cei cu nr-axSpA.*

Metode. *A fost realizat un studiu retrospectiv pe 266 de pacienți cu axSpA. Pacienții au fost clasificați în 2 grupe AS și nr-asSpA. Întârzierea diagnosticului s-a referit la timpul de la debutul durerii lombare și diagnosticarea axSpA. Specialitatea mdicului la care pacientul s-a prezentat inițial și primul diagnostic primit de către pacient au fost luate în considerare. Au fost comparate și alte date clinice și paraclinice între cele două grupuri.*

Rezultate. *Întârzierea diagnosticului a fost semnificativ mai mare la pacienții cu AS (6 ± 8.14 ani vs 1.62 ± 2.54 ani). 40.9% dintre pacienți au fost consultați inițial de medici cu specialitatea de recuperare medicală. 29.7% au fost consultați de neurochirurg și 19.9% de către reumatologi. Cel mai frecvent diagnostic inițial a fost fibromialgia (140 pacienți, 52.6%) urmat de AS (77 pacienți, 28.9%) și hernie de disc (34 pacienți, 12.7%).*

Concluzii. *Majoritatea pacienților nu au fost inițial evaluați de reumatologi și diagnosticul pus cel mai frecvent a fost de fibromialgie. Trebuie realizate eforturi astfel încât să se scurteze timpul până la corecta diagnosticare a axSpA.*

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