REASONS FOR DIAGNOSTIC DELAYS OF AXIAL SPONDYLOARTHRITIS

Robert Zwolak, Dorota Suszek, Aleksandra Graca, Marcin Mazurek, Maria Majdan
DEPARTMENT OF RHEUMATOLOGY AND CONNECTIVE TISSUE DISEASES, MEDICAL UNIVERSITY OF LUBLIN, LUBLIN, POLAND

ABSTRACT
Introduction: The probability of development of axial spondyloarthritis (axSpA) is estimated to be above 90% among patients with chronic back pain, presence of HLA B27 antigen and positive family history of ankylosing spondylitis (AS), psoriasis, reactive arthritis, inflammatory bowel disease or uveitis. The nonradiographic axSpA and ankylosing spondylitis diseases’ activity has a comparable impact on the patients’ quality of life and from the practical point of view the approach to treatment of each of them is the same.

The aim: The attempt to identify the reasons of diagnostic delays of AS among patients hospitalized in the Rheumatology and Connective Tissue Diseases Department in Lublin and to suggest the ways of improving the accuracy of diagnostic track among other healthcare providers than rheumatologists.

Material and methods: We performed a retrospective analysis of the records of 82 patients’ with the established diagnosis of AS, hospitalized in the Rheumatology and Connective Tissue Diseases Department in Lublin in 2000-2019, and of 45 years of age and older.

Results: From among 82 patients (28 women and 54 men) the diagnosis of AS after 45 years of age was established in 25 patients (10 women and 15 men) – group t, and in the other 57 patients (group n) the diagnosis was established before 45 years of age. On average the age at the time of diagnosis in the whole group (t+n) was 40,7±10,2 (18-76) years, the age at the beginning of inflammatory back pain (age of axial symptoms) was 30,9±8,5 (13-51) years and the diagnostic delay (period between first axial symptoms and diagnosis establishment) was 9,75±9,5 (0-46) years. We did not find any statistically significant associations between sex and age at the moment of diagnosis, age of the beginning of axial symptoms and the time of diagnostic delay. There was no significant difference of incidence of enthesitis, uveitis, arthritis, prevalence of family history of spondyloarthritis and CRP level between group t and n. Antigen HLA B27 was more frequently present in group t.

Conclusions: Instead of the recognition progress and worldwide popularization of knowledge about axSpA, the diagnostic delays in this field are still estimated to last many years, the patients are looking for other specialists’ help, and they can be not knowledgeable of the inflammatory back pain criteria. Currently, HLA B27 antigen and C-reactive protein are the two most commonly used biomarkers for diagnostic and disease activity monitoring purposes of axSpA and magnetic resonance is the only “imaging biomarker”.

The presence of extra-axial symptoms does not improve the diagnostic sensitivity.

KEY WORDS: axial spondyloarthritis, ankylosing spondylitis, sacroiliitis

INTRODUCTION
The term ankylosing spondylitis (AS) was created in 1900, and the disease was diagnosed on the basis of clinical symptoms in patients with advanced limitation of mobility of the spine. In the thirties of the last century, in the era of evolving X-ray diagnostics, it was proved that the inflammatory process initially develops in the sacroiliac joints [1]. The modified New York criteria from 1984 are based on the X-ray assessment of the sacroiliac joints. However, they reflect the late phase of the disease, identifying structural changes resulting from chronic post-inflammatory changes, not actually detecting active inflammation [2, 3].

The ASAS (Assessment of Spondyloarthritis International Society) group proposed the term non-radiial axial spondyloarthritis (nraxSpA) and its classification criteria in 2009 aimed to early identification of patients with spondylitis prior to irreversible radiological changes in the sacroiliac joints and spine instead of the previous ESSG criteria (European Spondyloarthropathy Study Group) from 1991 and Amor’s criteria from 1990 [4-6]. The new ASAS criteria have a sensitivity of 82.9% and a specificity of 84% compared to 70.7% and 63.5% or 69.4% and 78.4% for ESSG criteria and Amor criteria, respectively.

The probability of the development of the axial form of spondyloarthritis is over 90% in patients with chronic back pain, the present HLA B27 antigen and the positive family history in the direction of AS, psoriasis, reactive arthritis, inflammatory bowel diseases or uveitis [3]. The activity of the disease in the form of nraxSpA and AS similarly affects the quality of life, and from a practical point of view the approach to the treatment is the same [7]. In the light of the ASAS group criteria, chronic back pain typically occurs before the age of 45 in 90% - 95% of patients (on average, aged 25-28). Early treatment of nraxSpA relieves symptoms of the disease, improves spine mobility and reduces the severity of inflammatory changes detected in the magnetic resonance imaging (MRI) of the spine and sacroiliac joints [7]. The incidence of spondyloarthritis in the world depends on the presence of HLA B27 antigen in the population, which is found in white people in 4.6-7.5% and in black - in 1.1% of the total population. It should be emphasized that diseases related to the presence of HLA B27 antigen have a comparable impact on the patients’ quality of life and from the practical point of view the approach to treatment of each of them is the same.
of HLA B27 antigen affect only 8% of people possessing this antigen [8].

The ratio of men to women suffering from AS is 2 : 1 and in nraxSpA - 1 : 1, which indicates that women later or less often develop structural changes than men [1]. However, male gender has not been a better predictor of a good response to the treatment with anti-TNF molecules in AS and nraxSpA [9].

Sampaio-Barros et al. observed that the progression rate of the nrSpA form towards AS in 2 years is 10% and 24.3% in 5-10 years. It increases with age and in the group of patients with active inflammatory changes in the MRI of sacroiliac joints and/or increased concentration of reactive protein C (CRP) increases to 20-24% in 2 years [10, 11]. The ASAS classification criteria include only radiographic changes or in the MRI only changes located in the sacroiliac joint region and not in other parts of the axial skeleton. Inflammation within the spine may be present in 12% - 70% of patients with no changes in the sacroiliac joints. The structural changes in the form of erosions are not taken into account in the diagnosis of axSpA in the absence of active inflammation manifested as bone marrow edema [12, 13]. Histopathological evaluation of tissues taken from the same sites indicated by MRI as an active arthritis indicates low sensitivity of MRI [14]. In addition, fluctuation during inflammatory changes in the spine and sacroiliac joints indicates that initially the normal MRI can be positive - showing typical inflammatory changes in the joints later [15]. At the same time, numerous studies have shown a poor correlation between changes in the MRI and clinical symptoms [16-18].

In our work, we discuss the causes of late or abnormal diagnoses of AS in patients hospitalized in the Department of Rheumatology and Connective Tissue Diseases in Lublin and suggestions for improving the sensitivity of the diagnostic track, especially among doctors of other specialties than rheumatologists.

**MATERIALS AND METHODS**

History records of 82 patients (≥45 years old) with AS hospitalized in the Rheumatology Department of Medical University of Lublin in the years 2000-2019 were retrospectively analyzed.

Statistical analysis of the obtained results was carried out using the STATISTICA 13.1 computer program from StatSoft. For quantitative purposes, the arithmetic mean, standard deviation (SD) and the minimum and maximum values were calculated. The Manna-Whitney tests for the values presented on the quotient scale and the significance test of differences for the values presented in the nominal scale were used to assess the differences between groups.

**RESULTS**

Out of 82 patients (28 women and 54 men), the diagnosis of AS after 45 years of age was established in 25 patients - 30.4% (10 women and 15 men) - group t, in the remaining 57 patients (group n) diagnosis was established before the age of 45.

### Table 1. Age dependences at the time of diagnosis, the age of onset of axial symptoms and the time of diagnosis delay between the t and n groups.

<table>
<thead>
<tr>
<th>Age at the time of diagnosis</th>
<th>The age of onset of axial symptoms</th>
<th>The time of diagnosis delay</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group t (25pts)</strong></td>
<td>52.5 ± 6.0</td>
<td>35.1 ± 9.7</td>
</tr>
<tr>
<td><strong>Group n (57pts)</strong></td>
<td>35.4 ± 6.6</td>
<td>29.1 ± 7.3</td>
</tr>
</tbody>
</table>

| p                           | P = 0.0000001                    | P = 0.003                   | P = 0.000001                 |

Group t – the diagnosis of AS was established after 45 years of age
Group n – the diagnosis of AS was established before the age of 45

### Table 2. Associations regarding the incidence of HLA B27 antigen, tendonitis, uveitis, peripheral joints inflammation, positive family history of spondyloarthritis and elevated CRP concentration between t and n groups.

<table>
<thead>
<tr>
<th>Incidence of HLA B27 antigen (%)</th>
<th>Tendinitis present or history (%)</th>
<th>Uveitis present or history (%)</th>
<th>Peripheral joints inflammation present or history (%)</th>
<th>Positive family history of HLA-B27-dependent diseases (%)</th>
<th>Elevated CRP concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group t (25)</strong></td>
<td>22 (96.0)</td>
<td>6 (26.0)</td>
<td>10 (40.0)</td>
<td>13 (52.0)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18 (72.0)</td>
</tr>
<tr>
<td><strong>Group n (57)</strong></td>
<td>40 (75.5)</td>
<td>10 (17.5)</td>
<td>15 (26.3)</td>
<td>24 (42.1)</td>
<td>6 (11.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>48 (84.2)</td>
</tr>
</tbody>
</table>

| p                               | P = 0.03                         | NS                            | NS                                                  | NS                                                    | NS                             |

Group t - the diagnosis of AS was established after 45 years of age
Group n – the diagnosis of AS was established before the age of 45.
In subgroup analysis, the age at the onset of the first axial symptoms was 35.1±9.7 years in group t and 29.1±7.3 years in group n, whereas the delay in diagnosis was 18±11.3 and 6.2±5.7 years, respectively. There were no statistically significant correlations between gender and age at diagnosis, the age of onset of axial symptoms and the delay of diagnosis. There were no significant correlations between the incidence of tendinitis, uveitis, peripheral artery inflammation, inflammatory spondyloarthritis diseases, and CRP concentration between the t and n groups. HLA B27 antigen was more often present in the t group. Age dependences at the time of diagnosis, the age of onset of axial symptoms and the time of diagnosis delay between the t and n groups are shown in Table 1.

Associations regarding the incidence of HLA B27 antigen, tendonitis, uveitis, peripheral joints inflammation, positive family history of spondyloarthritis and elevated CRP concentration between t and n groups are presented in Table 2.

DISCUSSION
A delay in the diagnosis or inappropriate treatment of axSpA may lead to a decrease in the quality of life and in life expectancy of patients as well as long-term adverse consequences in the form of irreversible damages to the spine, peripheral joints, vision organs, aorta, osteoporosis and amyloidosis [19]. The incidence of axSpA in the population is estimated at 0.9% - 1.4% and the diagnosis delay is estimated even at 14 years [20, 21]. The disease can be diagnosed earlier if a suitably selected group of patients is referred to the rheumatologist. Only 37% of patients with ankylosing spondylitis in the United States are diagnosed by rheumatologists, the remaining 63% by family doctors (26%), physiotherapists (7%), orthopedists (4%), pain specialists (4%), by hospital emergency departments (3%) and other health care units (19%) [21]. A number of causes have been identified that lead to delayed diagnoses of axial spondyloarthritis, including AS. Spinal pain is common, affects 80% of adults at some point in their life. 13% of adults experience chronic pain, and only 5% of these patients have inflammatory pain [22, 23]. Patients very often seek help from other specialists who do not focus on inflammatory back pain. Unfortunately, these doctors may be unfamiliar with the criteria of inflammatory back pain.

Another problem is the objective assessment of spinal and sacroiliac joints, as opposed to peripheral joints. None of the physical backbone tests, including the measurement of spinal mobility, distinguishes inflammation of the spine joints from abnormalities found in the osteoarthritis [24, 25].

At present, the only biomarkers used in the diagnosis and monitoring of the activity of spondyloarthritides are HLA B27 presence and CRP concentration, respectively and MRI is the only “imaging biomarker”. The presence of HLA B27 antigen may be associated with faster progression of the disease and direct to the proper diagnosis. Observations from Seo and colleagues and our results do not confirm this relationship [26]. The HLA B27 antigen was more frequently observed in the group of patients diagnosed with AS after the age of 45 and thus with the longest delay.

The authoritative and reproducible interpretation of X-ray and MRI images of sacroiliac joints between different radiologists and the lack of joint training of radiologists and rheumatologists is of great difficulty. The X-ray of the sacroiliac joints has very low sensitivity in the early forms of spondyloarthritis. The specificity in the identification of inflammation in the MRI is also low, and foci of bone marrow edema may appear in healthy, physically active young adults, after trauma, in overload syndromes and degenerative disease joints [27-29]. Uncritical assessment of MRI images can lead to overinterpretation of results and false positive diagnoses.

In the patient population we examined, the diagnosis delay was 9.7 ± 9.5 years. There were no statistically significant correlations between the groups diagnosed with AS before and after the age of 45, and the presence of tendinitis, uveitis, peripheral joint inflammation, family history for spondyloarthritis and elevated CRP. Similar observations are confirmed by other researchers [26, 30, 31]. Different conclusions were presented by Dincer et al., who demonstrated a shorter delay period in the diagnosis of axSpA among patients with a positive history towards AS [31].

CONCLUSIONS
Delay in the diagnosis of axSpA, especially the non-radiological form, which very often leads to the development of AS, remains a challenge for modern rheumatology. Despite advances in diagnostics and greater dissemination of knowledge about spondyloarthritis, the delays in diagnosing these diseases are long-term, because patients very often seek help from other specialists who do not focus sufficiently on the criteria of back pain. Popularization of the ASAS axSpA criteria among specialists other than rheumatologists, especially the features of spinal inflammatory pain, HLA B27 antigen determination, wider access to the MRI of the sacroiliac joints and spine, and early referral for a rheumatologist may improve the diagnostic sensitivity of axSpA, allow rapid treatment and protect the patient against irreversible damages to the musculoskeletal system. Special attention is required for young patients with chronic back pain, the current HLA B27 antigen and family history of HLA B27 dependent diseases. The occurrence of extra-axial symptoms does not improve the diagnostic sensitivity.

REFERENCES


27. Deodhar A. Sacroiliac joint magnetic resonance imaging in the diagnosis of axial spondyloarthritis: “a tiny bit of white on two consecutive slices” may be objective, but not specific. Arthritis Rheumatol 2010;68:775–778.


ORCI numbers:
Robert Zwolak – 0000-0002-5160-6390
Donorza Suszek – 0000-0001-8131-6709
Aleksandra Graca – 0000-0003-3331-8763
Marcin Mazurek – 0000-0002-5352-5017
Maria Majdan – 0000-0002-4345-1675

Conflic of interest:
There is no conflict of interest.

CORRESPONDING AUTHOR
Robert Zwolak
Department of Rheumatology and Connective Tissue Diseases, Medical University of Lublin, Jacezkiewskiego Street 8, 20-090 Lublin
tel.: +48817244790, fax +48817244271
e-mail: zwolakr@wp.pl

Received: 06.02.2019
Accepted: 18.07.2019