MAY WE USE ENTHESITIS INDICES IN EVALUATING DISEASE ACTIVITY IN PATIENTS WITH ANKYLOSING SPONDYLITIS?

ESRA ERKOL İNAL¹, PINAR EROĞLU² İSMİHAN SUNAR³, SULTAN ÇANAK¹, MAHMUT YENER¹
¹Süleyman Demirel University, Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Isparta - ²Ankara Occupational Disease Hospital, Department of Physical Medicine and Rehabilitation, Ankara - ³Ankara University, Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Division of Rheumatology, Ankara, Turkey

Introduction

Ankylosing spondylitis (AS) is a chronic systemic inflammatory disease of unknown etiology. It especially affects the axial skeleton and is characterized by sacroiliitis¹. The prevalence of AS appears to vary among ethnic groups ranging from 0.1% to 6.0%. In Turkey the AS prevalence is found to be 0.45% and it is more than that in several European countries²-⁹.

Evaluation of disease activity in AS is very difficult due to lack of exhaustive relationship between acute phase reactants, clinical variables and imaging with disease process¹⁰-¹⁴. Although many instruments have been developed to assess signs and symptoms, there is not a gold standard procedure to define the disease activity¹³. The Assessment in Ankylosing Spondylitis (ASAS) International Working Group has defined acute phase reactants such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), The Bath Ankylosing Spondylitis Functional Index (BASFI) and Dougados Functional Index (DFI). Clinical status was evaluated with Bath Ankylosing Spondylitis Metrology Index (BASMI) and quality of life was assessed with Ankylosing Spondylitis Quality of Life Scale (ASQoL). We assessed enthesitis by two indices: Mander Enthesitis Index (MEI) and Maastricht Ankylosing Spondylitis Enthesitis Score (MASES).

ABSTRACT

Aims: The objective of the present study was to investigate the parameters related to disease activity in patients with Ankylosing Spondylitis (AS).

Materials and methods: Fifty-three patients with AS who fulfilled the modified New York criteria were included in this study. The demographic data of the patients were recorded. Laboratory evaluation of the patients comprised erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Disease activity was assessed using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Functional disability was evaluated using The Bath Ankylosing Spondylitis Functional Index (BASFI) and Dougados Functional Index (DFI). Clinical status was evaluated with Bath Ankylosing Spondylitis Metrology Index (BASMI) and quality of life was assessed with Ankylosing Spondylitis Quality of Life Scale (ASQoL). We assessed enthesitis by two indices: Mander Enthesitis Index (MEI) and Maastricht Ankylosing Spondylitis Enthesitis Score (MASES).

Results: The patients were divided into two groups: patients having BASDAI scores of less than four (BASDAI<4) with mild disease activity (N=42) and patients having BASDAI scores of four or higher (BASDAI≥4) with moderate to severe disease activity (N=11). MEI, MASES and BASFI scores were significantly higher in patients with moderate to severe disease activity. No significant difference was found in terms of CRP, BASMI and ASQoL between the two groups. A significant correlation was found between the BASDAI scores and MEI, MASES, CRP, DFI and BASFI in patients with AS (the correlation coefficients were 0.538, 0.544, 0.328, 0.407 and 0.466 respectively. P values were <0.05 for all).

Conclusions: Laboratory findings are not enough to evaluate disease activity in AS. However CRP seems to have better correlation with disease activity than ESR does and MASES and MEI seem to be an appropriate surrogate for disease activity in AS patients.

Key words: Ankylosing spondylitis, disease activity, quality of life, enthesitis, acute phase reactants.

Received February 18, 2014; Accepted June 19, 2014
elevated levels of commonly used acute phase reactants (ESR and CRP)(12,13,16) or also high scores of BASFI(13-15) or enthesitis indices(17,18) with disease activity have been reported only in a few papers and they have not been fully understood yet. Therefore, in this study, we aimed to evaluate the associations between some acute phase reactants, quality of life, clinical measures, enthesitis indices and disease activity in patients with AS.

Materials and methods

Fifty-three patients with AS (female 17, male 36) who fulfilled the modified New York criteria(19) were included in this study from our outpatient clinic. Informed consents of the patients were obtained before attending the study. The demographic data including age, sex, onset of first symptom, duration since diagnosis and start of the medication were recorded. All of the patients were on one of non-steroidal anti-inflammatory drugs and/or sulphasalazine 2-3gr/day and/or biologic agents.

Visual analog scale (VAS) was used to determine intensity of pain, patient’s global assessment and physician’s global assessment of the illness (0-10 cm, 0=no pain and 10=severe pain). Laboratory evaluation of patients comprised ESR and CRP.

The disease activity was assessed using the Turkish version of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). BASDAI is a self-administered questionnaire consisting of six questions relating to five major symptoms including fatigue, spinal pain, joint pain/swelling, areas of localized tenderness and morning stiffness. Morning stiffness was measured in terms of both severity and duration. In each of the five questions, the patients were asked to rate pain they felt over the previous week on a 10 cm horizontal VAS, while the scale for degree of morning stiffness is graded in every 15 minutes during a period of 0-2 hours. The mean of two scores of morning stiffness is calculated. VAS has no distinguishing marks except the words ‘easy’ at one end and ‘impossible’ at the other end of the line to indicate the direction of severity. Total BASDAI score is the mean of the total of five scores with higher scores indicating higher disease activity(12,13,16).

The severity of enthesitis was evaluated by Mander Enthesitis Index (MEI) and MASES(24,25). Enthesitis were evaluated by firm palpation with the pulp of the thumb (the amount of pressure required to blanch thumbnail). In MEI, the scores were recorded according to severity of the tenderness (0=no pain; 1=mild tenderness; 2=moderate tenderness; 3=wince or withdraw). Sixty six enthesis points were palpated and they were as follows: the nuchal crests, the manubriosternal joint, the costochondral joints, the greater tuberosity and the lateral and medial epicondyles of the humerus, the iliac crests and the anterior superior

Functional disability was evaluated using the Turkish version of BASFI and dougados functional index (DFI). BASFI consists of eight questions on daily activities and two additional questions to assess patients’ ability to cope with everyday life. Each question was answered on 0-10 cm horizontal VAS, reflecting status over the previous month. The VAS have no distinguishing marks except the words ‘easy’ at one end and ‘impossible’ at the other end of the line to indicate the direction of severity. BASFI score is the mean of the total of ten scores, with higher scores indicating more severe impairment. DFI consists of twenty items assessing the ability to perform different daily activities. The questionnaire provides three types of answers for scoring as: 0 (yes, with no difficulty), 1 (yes, but with difficulty), and 2 (no). The total score is calculated as sum of the twenty grades (ranging from 0 to 40), with higher scores indicating more severe impairment(23).

Clinical status was evaluated with Bath Ankylosing Spondylitis Metrology Index (BASMI). BASMI was calculated with the measurements of wall to tragus distance, lumbar flexion, cervical rotation, lumbar lateral flexion, and intermalleolar distance. Lateral flexion of lumbar spine was measured bilaterally and the mean of right and left flexion values were accepted as a single value. Each measurement received either 0 (mild disease involvement), 1 (moderate disease involvement), or 2 (severe disease involvement) points. The sum of five scores is 0-10 with higher scores indicating higher disease involvement(23).

Quality of life was assessed with the Turkish version of Ankylosing Spondylitis Quality of Life scale (ASQoL). ASQol comprises 18 items and each item was scored either 1 or 0. The total score range from 0 to 18, with a higher score indicating poor quality of life(23).

The severity of enthesitis was evaluated by two indices: Mander Enthesitis Index (MEI) and MASES(24,25). Enthesitis were evaluated by firm palpation with the pulp of the thumb (the amount of pressure required to blanch thumbnail). In MEI, the scores were recorded according to severity of the tenderness (0=no pain; 1=mild tenderness; 2=moderate tenderness; 3=wince or withdraw). Sixty six enthesis points were palpated and they were as follows: the nuchal crests, the manubriosternal joint, the costochondral joints, the greater tuberosity and the lateral and medial epicondyles of the humerus, the iliac crests and the anterior superior
iliac spines, the greater trochanter of the femur, the tibial tuberosities, the adductor tubercles, the medial and lateral condyles of the femur and tibia, the head of the fibula, the calcaneal insertions of the plantar fascia and the achilles tendons, the sacroiliac joints, the cervical, thoracic and lumbar spinous processes, the ischial tuberosities, and the anterior posterior iliac spines. Some of the sites were scored individually whereas others were recorded as a group which were: the nuchal crests, the costochondral joints, the sacroiliac joints, and the cervical, thoracic and lumbar spinous processes. The remaining sites were scored individually left and right. Total maximum possible score is 90\(^{24}\). In MASES which is more time saving in comparison with MEI, 13 enthesitis sites, which are the fifth lumbar spinous process and both sides of first and seven costochondral joints, posterior superior iliac spine, anterior superior iliac spine, iliac crest and achilles tendon insertion, were examined and presence or absence of tenderness was noted. The total score range from 0 to 13\(^{25}\).

### Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) software version 15.0 for Windows (SPSS Inc., Chicago, IL). Frequencies and percentages were used for categorical data. For comparison of quantitative variables, suitability of parametric test conditions was checked. For variables which met parametric test conditions, Student’s t test and for other variables Mann-Whitney U test were used for two group comparisons. For evaluation of categorical variables, chi-square (X\(^2\)) test and if needed, Fisher’s exact test were used. Pearson correlation coefficient was used to investigate correlations between variables and correlations were demonstrated as scatter diagrams. Multiple linear regression analysis was conducted to evaluate the associations between dependent variable (BASDAI) and potentially predictive variables (MASES, MEI, CRP, BASFI, DFI) and P<0.05 was accepted as significant for all statistical analyses.

### Results

The mean age of patients was 41.13±12.56 years and mean duration since diagnosis was 98.70±92.48 months. The laboratory and clinical characteristics of the patients are summarized in table 1.

<table>
<thead>
<tr>
<th>Mean ± SD</th>
<th>Min - max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>41.1±12.6</td>
</tr>
<tr>
<td>Onset of first symptom (month)</td>
<td>156.4±115.4</td>
</tr>
<tr>
<td>Duration since diagnosis (month)</td>
<td>98.7±92.5</td>
</tr>
<tr>
<td>Duration since start of medication (month)</td>
<td>95.9±91.4</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>23.1±15.8</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>10.4±12.6</td>
</tr>
<tr>
<td>VAS Pain</td>
<td>3.6±1.9</td>
</tr>
<tr>
<td>VAS patient’s global assessment</td>
<td>3.6±1.8</td>
</tr>
<tr>
<td>VAS physician’s global assessment</td>
<td>3.3±1.8</td>
</tr>
<tr>
<td>BASMI</td>
<td>1.4±0.4</td>
</tr>
<tr>
<td>BASFI</td>
<td>1.5±1.4</td>
</tr>
<tr>
<td>BASDAI</td>
<td>2.6±1.8</td>
</tr>
<tr>
<td>DFI</td>
<td>4.5±5.2</td>
</tr>
<tr>
<td>ASQoL</td>
<td>2.8±4.3</td>
</tr>
<tr>
<td>MEI</td>
<td>2.5±5.0</td>
</tr>
<tr>
<td>MASES</td>
<td>0.7±1.7</td>
</tr>
</tbody>
</table>

Table 1: The laboratory and clinical characteristics of patients with AS (n=53).


The patients were divided into two groups: patients having BASDAI scores of less than four (BASDAI<4) with mild disease activity (N=42) and patients having BASDAI scores of four or higher (BASDAI≥4) with moderate to severe disease activity (N=11). MEI, MASES, BASFI, VAS pain, VAS patient’s and physician’s global assessment scores were significantly higher in patients with moderate to severe disease activity (p<0.05 for all). No significant difference was found in terms of ESR, CRP, BASMI, DFI and ASQoL between both groups. The laboratory and clinical characteristics of the groups are summarized in table 2.

There was a significant correlation between BASDAI score and VAS pain, VAS patient’s and physician’s global assessment and correlation coefficients were 0.864, 0.818 and 0.860 respectively and P values were <0.001 for all. A significant correlation was found between the BASDAI scores and MEI, MASES, CRP, DFI and BASFI. The correlation coefficients were 0.538, 0.544, 0.328, 0.407 and 0.466 respectively and P-values were <0.05 for all.
Correlations between BASDAI scores and clinical, functional, quality of life and laboratory parameters and enthesitis indices in patients with AS are shown in table 3.

In multiple linear regression analysis, MASES, DFI and CRP with 53.1% ratio were the best predictors for BASDAI scores. The results of regression models are summarized in table 4.

Discussion

Bath Ankylosing Spondylitis Disease Activity Index is commonly used to evaluate disease activity in AS. BASDAI is a composite patient derived index and a widely used subjective measure of disease activity that was proved to be valid, reproducible and responsive to change (11). Spoorenberg et al. evaluated disease activity in AS patients using patients’ and physicians’ perspectives. When patients and physicians were asked to assess the disease activity, patients focused on subjective complaints whereas physicians focused on clinical and laboratory findings related to the severity of the disease (13). Patients with AS only have axial involvement in varied severity but may also have peripheral joint involvement and extraspinal manifestations like enthesitis, uveitis etc. These variations in clini-
cal symptomatic make evaluation of the disease activity in patients with AS difficult and still there is no objective gold standard for this issue(26).

Measurement of acute phase proteins can be powerful assessment tool for diagnosing and monitoring inflammatory diseases. Although acute phase reactants such as ESR and CRP are widely being used parameters, it has been shown that they have limited value in evaluating disease activity of patients with AS in several studies(12, 13, 16, 18, 24). ESR and CRP were also reported to not have a role in evaluation of the disease activity in AS(12, 26). In our study it was shown that CRP seems to have a better correlation with disease activity than ESR similar to Bostan et al.(27).

BASFI and DFI have been recommended by ASAS Working Group for evaluating physical function in core sets(15). In the previous studies it was shown that disease activity of AS is related with functional capacity and quality of life(27-29). Previously it was reported significantly higher BASFI and poorer ASQoL scores in the patients with higher BASDAI scores (≥4) compared with lower BASDAI scores (<4)(30). A significant correlation between BASDAI scores with BASFI and ASQoL was also reported(30). Similarly, a significant relationship between BASDAI scores with BASFI and DFI has been shown(25). In the present study BASFI scores were higher in the patients with moderate to severe disease activity and BASDAI scores were significantly correlated with BASFI and DFI scores consistent with the previous studies. But unlikely, no significant relation was found between ASQoL and BASDAI scores in our study.

Enthesitis is a characteristic histopathological feature of AS(20). Enthesitis sides are known to be active regions where inflammatory disease develops in patients with AS(32). Obviously, ESR and CRP alone are not effective in evaluating the disease activity in patients with AS. To evaluate the disease activity, clinical data were needed, and thus, enthesitis indices were added to evaluation parameters by ASAS International Working Group(15). Heuft-Dorenbosch et al. reported that in patients with AS, peripheral joint involvement might have affected the BASDAI scores and also found a correlation between MEI and BASDAI scores(25). The relationship between MEI and MASES and BASDAI scores was reported in several studies(14, 17). Similarly, in our study a significant correlation was found between MEI, MASES and BASDAI scores.

Enthesitis index was accepted to be a valuable tool in the evaluation of disease activity in patients with AS. However evaluation of enthesitis severity is based on information given by patient and should be combined with objective parameters when assessing disease activity(18). Likewise, we have demonstrated that enthesitis indices, DFI and CRP have determinative impacts on BASDAI scores which are being used to define disease activity of AS today.

Our results partially were in contrast with previous studies. Recently the male to female ratio in patients with AS was reported as 3.02/1 in Turkish population(33), but in our study it was 2.11/1. This diverse ratio of male to female in patients with AS might have caused different results. One of the limitations of this study is relatively smaller number of the patients.

In this study enthesitis indices and BASDAI were well correlated as in the previous studies(14, 17, 20). Assessment of enthesitis remains to be a valuable tool in evaluation of AS patients. MASES and MEI can be used to give an opinion about disease activity in patients with AS. However enthesitis indices are subjective measurements. Therefore we concluded that, in order to evaluate disease activity of patients with AS, enthesitis indices, especially MASES which is shorter and more time saving, should be combined with objective parameters like CRP or ultrasonographic assessment of enthesitis. Further investigations in this field are needed to enlighten this issue.

References


Corresponding Author
ESRA ERKOL İNAL, PINAR EROĞLU et al
Süleyman Demirel University Faculty of Medicine, Department of Physical Medicine and Rehabilitation
Çünü̇r, İsparta
(Turkey)