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ORIGINAL ARTICLE

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In ankylosing spondylitis serum interleukin-6 correlates with the degree of mobility restriction, but not with short-term changes in the variables for mobility

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Abstract The aim of this study was to evaluate whether the serum concentration of interleukin-6 (IL-6) reflects disease activity in ankylosing spondylitis (AS). A group of 271 AS patients were enrolled in the study, 261 of whom completed the entire protocol (201 males, 60 females, median age of 53 years). Serum IL-6 was measured three times (I, baseline; II, after 10–12 days; III, after 17–24 days) during a 3- or 4-week treatment at the health resort. At the same times, the variables for mobility were measured, and the patients were asked to assess their complaints (score) in a self-styled questionnaire. The serum concentration of IL-6 correlated with the measurements of occiput-to-wall distance, cervical rotation, finger-floor distance and Schober sign, and with morning pain at all three evaluations. Comparisons between changes in IL-6 and changes in the variables (measures of mobility, scores of the questionnaires) did not reveal significant correlations. Present data would suggest that in AS the serum concentration of IL-6 indicates the degree of mobility restriction resulting from previous disease progression, but is not a reliable marker of current disease activity.

Key words Ankylosing spondylitis · Interleukin-6 · Disease activity · Severity · Mobility

Introduction

Various instruments have been developed to assess disease activity, mobility, function, outcome and global status in ankylosing spondylitis (AS) [1]. Using visual analogue scales, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) measures the degree of fatigue, joint pain, tenderness and morning stiffness felt by the patient [2]. It thus reflects the degree of subjective discomfort and pain caused by the disease. It is a validated tool as far as userfriendliness, reproducibility, measurement and sensitivity to change are concerned.

Another approach to defining disease activity is the measurement of laboratory variables. Gratacos et al. [3] reported that interleukin-6 (IL-6) is closely correlated with disease activity as measured by ESR, CRP, platelet count, visual analogue pain score, visual analogue stiffness score and the Schober test.

What does disease activity in ankylosing spondylitis mean? Is it the degree of discomfort felt by the patient? Is it a laboratory variable which, from other diseases, is known to reflect the magnitude of inflammation?

In our opinion these definitions are not very satisfying. Active disease in AS means there are ongoing pathological changes caused by the disease, which may contribute to disease progression in the near future. High activity over a longer period of time would then be associated with objective deterioration, i.e., particularly in AS, a decreased mobility due to alterations in bone, joint structures and ligaments. This highly active state is, of course, commonly associated with more severe complaints. There is no convincing evidence, however, that the severity of the complaints will allow a reliable prediction of disease progression, so that actual complaints of the patient should not be considered as a measure of disease activity.

Is IL-6 a reliable marker of disease activity? If IL-6 indicates the actual disease activity, it would be expected to parallel short-term alterations in symptoms and signs, i.e., changes in the serum concentration of IL-6 would closely correlate with changes in the severity of symptoms and signs.

In the present study we evaluated whether changes in the serum concentration of IL-6, a presumed marker of disease activity in AS, are correlated with changes in symptoms or mobility during a 3- to 4-week treatment period at a health resort.

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Materials and methods

Patients

A group of 271 patients with AS, who presented for a 3- or 4-week speleotherapeutic cure treatment at the Gasteiner Heilstollen (radon exposure in a former mine) gave their informed written consent to participate in this investigation. In three patients the treatment was discontinued because of side effects (bradycardia, dizziness, vaginal bleeding), in one patient, for private reasons (unrelated to therapy). Six patients refused the second or third blood test. We report results obtained with the remaining 261 patients, who completed the entire protocol: 201 males and 60 females, with a median age of 53 years (25th and 75th percentile: 45 and 60 years). AS had been diagnosed for a median of 15 years (9–25 years); symptoms of the disease had been present for a median of 25 years (18–33 years).

Measurement of mobility

Physical examination was performed by medical doctors experienced with the procedure. A flexible tape and a goniometer were used to measure occiput-to-wall distance, chin-chest distance, chest expansion, cervical rotation, finger-floor distance, Schober sign, and Ott sign (distance 30 cm caudal of prominence, change after maximum flexion, as described in [4].

Questionnaire

Typical symptoms of AS patients during the previous week were assessed using five specially designed questions (answers were given by patients and recorded by the examining doctor). The resulting score was used for calculations

A. Did you wake during the night?

Response:	No	Yes: 1	2	3	4	5	6 nights	Every night	Several times per night
Score:	0	1	2	3	4	5	6	7	8

B. Did you get out of bed because of symptoms of AS?

Response:	No	Yes: 1	2	3	4	5	6 nights	Every night	Several times per night
Score:	0	1	2	3	4	5	6	7	8

C. After rising in the morning complaints due to AS were:

Response:	Intolerable	Severe	Moderate	Slight	None
Score:	1	2	3	4	5

D. Walking on a level surface was:

Response:	Impossible	Poor	Impaired	Good	Very good
Score:	1	2	3	4	5

E. Mobility of the head was:

Response:	Impossible	Poor	Impaired	Good	Very good
Score:	1	2	3	4	5

Laboratory evaluation

ESR was measured by the Westergren method. Venous blood was centrifuged at 1500 *g*. Serum was frozen at –18 °C. Measurements were performed in one batch with commercially available test kits: CRP [mg/l] by turbidimetry, (Orion, Espoo, Finland); IL-6 (pg/ml) by ELISA (CLB, Amsterdam, Netherlands). CRP concentrations of less than 5 mg/l were taken as zero. The laboratory staff was not informed of the results of the physical examination.

Protocol

During the 3- to 4-week stay at the health resort the patients were treated 9–12 times in the gallery of the Gasteiner Heilstollen. Each stay in the gallery takes about 1 h (radon concentration of up to 4.5 nCi/l; temperature 38–41.5 °C; relative humidity 70–98%). Other therapies were also administered depending on the particular patient's needs (individual and group physiotherapy, hydrotherapy, massage therapy, etc.).

The examining physician filled out the questionnaire according to the patient's answers and measured mobility before the patient's first entry into the gallery (I), before his 5th or 6th entry (after 10–12 days: II), and before his 9th–12th entry into the gallery (between 17 and 24 days after the first examination: III). In more than 90% of the cases, the examinations took place at the same time of day (±2 h). On the same day (I, II and III) blood was taken from a peripheral vein for determination of ESR, CRP and IL-6.

At all three evaluations, the serum concentration of IL-6 was correlated with the absolute measurement values of mobility and the scores of the patient's subjective assessment (questionnaire). Also, the changes in IL-6 between evaluation I and II, and between I and III were correlated with the changes in these variables during the same periods.

Statistical analysis

The results of the first (I), second (II) and third (III) evaluations are given as mean±SEM. Differences between I and II and between I and III (intra-individual changes) were tested for significance using paired Wilcoxon tests.

At all three evaluations the significance of the correlation between the actual serum concentration of IL-6 and the actual degree of symptoms (questionnaire), of mobility and of CRP was tested using Spearman correlation tests.

The Spearman correlation test was also performed to test the significance of the correlation between changes in IL-6 and changes in symptoms (questionnaire) or in variables of mobility from evaluation I to II, and I to III.

A P value of <0.05 was considered significant. For interpretation it should be noted that the significance level was not adjusted for the number of calculations.

Results

The results of evaluations I, II and III are given in Table 1. Compared to the results of evaluation I, the ESR, all variables of mobility and all scores of the subjective assessment showed a significant improvement at evaluation III. The serum concentration of IL-6 did not change significantly.

A significant correlation between the serum concentration of IL-6 and the serum concentration of CRP was found at all three evaluations ($P<0.01$).

The correlation coefficients obtained from the Spearman test for all correlations between IL-6 and the respective variables at evaluation I, II and III are listed in Table 2. At all three evaluations the correlation between the actual serum concentration of IL-6 and the actual occiput-to-wall distance, the cervical rotation, the finger-floor distance and the score of question C (morning com-

Table 1 Results of laboratory tests, physical examination and the questionnaire at evaluations I, II and III (mean; SEM) in paired Wilcoxon tests comparing the results in evaluation II and III with the data at baseline (I)

	Evaluation I	Evaluation II	Evaluation III
ESR (h^{-1})	**12.6**; 0.75	**12.0**; 0.72 *	**11.9**; 0.71 **
CRP (mg/l^{-1})	**7.82**; 1.01	**7.14**; 0.73	**6.74**; 0.67
IL-6 (pg/ml^{-1})	**4.35**; 0.25	**4.41**; 0.27	**4.39**; 0.28
Occiput-wall (cm)	**7.04**; 0.54	**6.48**; 0.5 **	**6.27**; 0.52 **
Chin-chest (cm)	**4.51**; 0.16	**4.49**; 0.19	**4.22**; 0.17 **
Cervical rotation (°)	**90.2**; 2.69	**95.6**; 2.74 **	**98.3**; 2.85 **
Chest expansion (cm)	**3.3**; 0.11	**3.68**; 0.2 **	**3.67**; 0.13 **
Finger-floor (cm)	**23.4**; 0.99	**22.4**; 0.96 **	**21.8**; 0.96 **
Ott (cm)	**31**; 0.13	**31.2**; 0.07 **	**31.2**; 0.06 **
Schober (cm)	**12.3**; 0.09	**12.3**; 0.09	**12.4**; 0.1 **
Question A (score)	**2.61**; 0.21	**2.21**; 0.2 *	**1.49**; 0.16 **
Question B (score)	**1.48**; 0.17	**0.98**; 0.14 **	**0.74**; 0.12 **
Question C (score)	**3.54**; 0.06	**3.69**; 0.06 **	**3.95;** 0.05 **
Question D (score)	**3.84**; 0.05	**3.92**; 0.05	**3.95**; 0.05 *
Question E (score)	**3.12**; 0.06	**3.26**; 0.06 **	**3.38**; 0.06 **

* $P<0.05$; ** $P<0.01$

Table 2 Correlation (r_s) between serum IL-6 and the respective variable at evaluations I, II and III

Variables	Evaluation I	Evaluation II	Evaluation III
Occiput-wall	0.15 *	0.15 *	0.15 *
Chin-chest	0.20 **	0.20 **	0.08
Cervical rotation	–0.26 **	–0.23 **	–0.22 **
Chest expansion	–0.18 **	–0.18 **	–0.09
Finger-floor	0.14 *	0.17 **	0.18 **
Ott	–0.11	–0.16 *	–0.11
Schober	–0.16 *	–0.15 *	–0.09
Question A	0.12	0.09	0.10
Question B	0.06	0.03	0.03
Question C	–0.13 *	–0.25 **	–0.21 **
Question D	–0.14 *	–0.12 *	–0.04
Question E	–0.14 *	–0.13 *	–0.12

r_s = Spearman correlation coefficient; * $P<0.05$; ** $P<0.01$

plaints) was significant. All other comparisons between the IL-6 concentration and other actual variables did not reveal consistent significant correlations at all three evaluations.

There was a significant correlation between the change in IL-6 from I to II and the change in the score of question B from I to II ($r_s = 0.136$; $P = 0.028$). All other correlation tests between changes in IL-6 and changes in the variables (measures of mobility, scores of questions) were not significant ($P>0.05$) in any of the evaluations (Table 3).

Discussion

The serum concentration of IL-6 correlated with the measurements of occiput-to-wall distance, cervical rotation and finger-floor distance in all three evaluations. The results suggest a close association between IL-6 and the degree of mobility restriction. In AS, mobility restriction may result from both the severity (long-term changes due to disease progression, especially ossification) and the activity of the disease (ongoing changes, e. g., inflammation-induced stiffness).

Table 3 Correlation (r_s) between changes in the serum concentration of IL-6 (change from evaluation I to II, and change from I to III) and changes in the respective variables in the same period

Variables	r_s (I →II) [a]	r_s (I →III) [b]
Occiput-wall	0.01	0.04
Chin-chest	0.05	0.00
Cervical rotation	–0.11	–0.07
Chest expansion	–0.03	0.04
Finger-floor	0.10	0.00
Ott	–0.04	–0.00
Schober	–0.04	–0.07
Question A	0.09	0.07
Question B	0.14 *	0.06
Question C	0.03	–0.08
Question D	–0.06	0.02
Question E	–0.07	–0.01

* $P<0.05$

[a] r_s (I→II), correlation coefficient of changes in IL-6 from I to II/changes in each variable measurement from I to II

[b] r_s (I→III), correlation coefficient of changes in IL-6 from I to III/changes in each variable measurement from I to III

The changes in IL-6 were not associated with the changes in mobility during the same period. This lack of correlation would suggest that IL-6 does not reflect the current disease activity in AS, as it does not follow short-term changes in clinical variables, but seems to be closely related to the severity of the disease, which is the consequence of previous long-term progression.

This conclusion, however, is not as clear as the present data would suggest. When interpreting the results it must be kept in mind that both the serum concentration of IL-6 and the variables for mobility may have been influenced by the administered therapies. IL-6 concentrations may have been influenced by generalized hyperthermia during treatment in the gallery [5], and physical exercise may have improved mobility [6]. Nevertheless, the close correlation between IL-6 and the variables for mobility at all three evaluations is striking.

A significant correlation was observed between serum IL-6 and CRP in all three evaluations. Since CRP stimulates hepatic synthesis of CRP, this result is not surprising. In our opinion this finding does not permit IL-6 to be called a marker of disease activity in AS, as previously suggested [3].

Serum IL-6 was closely related to mobility restriction. It may be presumed that both the serum concentration of IL-6 and the degree of mobility restriction could be influenced by a third factor. We tested this presumption for age and disease duration, but neither was found to correlate with the serum concentration of IL-6 ($P = 0.26$ and $P = 0.4$, respectively).

Present data would suggest that the serum concentration of IL-6 is closely associated with the restriction of mobility resulting from previous disease progression. IL-6 does not seem to be a reliable marker of current disease activity in AS, as it does not correlate with short-term changes in clinical parameters.

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