STUDY OF CARDIO-PULMONARY ONSETS IN ANKYLOSING SPONDYLITIS

DOCTORAL THESIS

(Abstract)

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INTRODUCTION

Ankylosing spondylitis is a chronic inflammatory disorder of incompletely known aetiology, affecting usually men of young age, progressing to significant structural deteriorations by spinal mobility decrease, peripheral and extraarticular joints disorders, the consequence being the decrease of life and work productivity quality on these patients.

The major research issue that I have approached in this study is the evaluation of the frequency and the identification of the types of cardio-pulmonary disorder in patients with ankylosing spondylitis.

The ankylosing spondylitis is associated with the increase of morbidity and mortality through cardiovascular disease, a defined relationship existing between cardiovascular disorder and ankylosing spondylitis of which magnitude has not been established yet. The chronic inflammatory condition as well as other traditional risk factors are responsible for the escalation of the cardiovascular risk in those patients.

Pulmonary disorder is an onset tardily appearing during the disease progress and influencing the life quality and the prognostic of these patients through the restrictive ventilatory malfunction phenomena.

The work is structured by two parts: the general part which includes theoretical concepts regarding aetiology of the cardiovascular and pulmonary disorder and affectation, as well as clinico-imagistic appearance of the latter, concepts that are intended to support the importance of the chosen theme and the special part which includes: the study objectives, material and method, the results achieved following complex evaluation of patients with spondylitis, the discussion of the results which enabled drafting of conclusions having practical value.
MATERIAL AND METHOD

- STUDY PURPOSE AND OBJECTIVES
  *The major research issue* is the evaluation of the frequency and the pattern of the cardiovascular, pleuropulmonary affectation and identification of possible predictive factors in the occurrence and severity of these onsets.

- EXPLORATION PROTOCOL
  The study has a prospective character, of case-control type, being undertaken over a four year’s period, in the Rheumatology Clinics of the County Emergency Clinical Hospital of Craiova.

- PATIENTS’ SELECTION CRITERIA
  *Eligibility criteria*: New York modified diagnosis criteria (1984), IMC within normal cut-offs, associated cardiovascular, pulmonary or renal pathology absence.
  *Exclusion criteria*: sugar diabetes, arterial hypertension, over weight/obesity, sedentarism, smoking, lues antecedents, RAA, pulmonary tuberculosis, sarcoidosis, professional or habitual exposure to different environment agents (powders, asbestos, silica, gas).

- MONITORED PARAMETERS
  The study design supposed the recording of patients with spondylitis, diseases evolution duration, type of articular affectation (either axial or peripheral), disease progression, biological explorations (VSH, hsCRP, glycaemia, complete lipid profile, creatinine, uric acid),
activity scores (BASDAI), mobility and severity (BASFI), therapeutic protocol, standard radiological examination – sacroiliac joints and dorsolumbar junction, vertebral, lumbar, thorax, cervical spine, peripheral joints, standard EKG, cardiac and vascular echographic examination (including Doppler), thoraco-pleuro-mediastino-pulmonary radiography, PFV.

- **STATISTICAL ANALYSIS**

  The statistical analysis has used *statistic indicators* of the central tendency: arithmetical mean, module, median, data spread indicators: standard deviation, standard error of the mean, trust interval 95% of the mean, as well as the following *statistic tests*: square Chi test, Fisher exact test, ANOVA test, Student-Newman-Keuls test.

  Linear regression was used to describe the relationship between two variables and to be able to express predictions of the value of one depending on the other. The $r^2$ determination coefficient was expressed, F ratio and p value, of which statistic significance was accepted only for values under 0.05.

  The data base was administrated by using Excel program from the Microsoft Office package, and the statistical analysis benefited from statistically dedicated programs MedCalc and Epi Info 2000.
RESULTS AND DISCUSSIONS

- PATIENTS’ BATCH STRUCTURE
  The study group was made up of 140 subjects grouped depending on the type of disorder which determined the admission in 2 batches: patients with SA(70) and patients which showed up for non-inflammatory rheumatic disorders (degenerative or other nature), with the male gender preponderance (sex ratio (B/F) in the batch of cases it was 2.68), with a mean duration of disease evolution of 17.23 years (DS=9,39; IC95% 14,98-19,46).

- CLINICAL AND PARACLINICAL EVALUATION OF THE SUBJECTS INCLUDED IN THE STUDY
  With regard to IMC, TA and biochemical parameters that can increase the risk of cardiovascular affectation it has been found batches homogeneity. Total cholesterol, triglycerides, uric acid cut-offs are comparable for the two batches and are within normal range.

  Patients’ distribution depending upon the type of predominant osteoarticular affectation indicated a prevalence of the axial affectation (51%), and the assignment depending upon the disease stage showed a prevalence of the stage II and III.

  For the activity evaluation I have used the most important indicators which enable establishing the degree of activity – VSH, hsCRP, BASDAI, being recorded, regardless of the studied batch, cut-offs which are higher as compared to the physiological limits, in accordance with the degree of activity of the disease.

- PATIENT’S PROFILE WITH SA AND CARDIOVASCULAR AFFECTATION

  Aortic emergence dilation
  The dimensions of the aorta emergence were higher in the batch with SA, and the risk of aortic dilation over the normal cut-offs was different depending on the measurement site from the emergence level. Thus the highest risk was noticed at the level of the aorta ring.
(OR=12.67; IC95% 2.82-58.86; p=0.009), and the lowest at the level of the ascendant aorta (OR=5.02; IC95% 1.04-24.12; p=0.044). It has been identified a significant correlation with patients’ age, the disease evolution duration, the inflammatory status and the BASFI functional score, the most powerful impact being that of the disease evolution duration.

**Aortic and mitral valve affectation**

It has been noticed a higher incidence of aortic and mitral regurgitation in cases from the batch with ankylosing spondylitis and a correlation with the age of patients with SA, the diseases evolution duration, VSH cut-offs, hsCRP serum average levels, the BASDAI evaluation score of the disease activity and the BASFI score cut-off.

The study of *pressure in the pulmonary artery, of diastolic dysfunction of the left ventricle and of pericardial effusion* has proved an increased incidence in patients with SA as compared to the control subjects.

The study of the *electrocardiographic abnormalities* has identified an increased incidence of driving disorders as compared to the witness batch, but statistically insignificant. Instead, a statistically significant difference has been noticed between the mean of the QT interval cut-offs in cases of patients with SA, as compared with the control subjects.

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**PROFILE OF PATIENTS WITH ACCELERATED ATHEROSCLEROSIS**

- *Appreciation of endothelial dysfunction as inaugural event in atherosclerosis sequences through IMT quantification at the level of the carotid arteries*

  Endothelial dysfunction presence as inaugural event in atherosclerosis sequences, detected from ahead of time through the quantification of the intima-media thickness at the level of the joint carotid arteries has been proved in 34.29% of cases of patients with SA
(24 cases), as compared to the witness batch, where only 5.71% of the control subjects (4 cases) showed increased cut-offs surpassing the normal range considered in the study of the IMT. It has been found a statistically significant influence of the inflammatory condition, of patients’ age, of the diseases evolution duration and of the BASFI evaluation score of the disease severity, on the increase of the risk to occur endothelial dysfunction in these patients.

By the exclusion criteria I have tried to remove other risk factors for the atherosclerotic vascular affectation, respectively smoking, high blood pressure, obesity, obvious dyslipidemia, sugar diabetes. When we refer to the metabolic profile of the patients included in the study, the total cholesterol cut-offs, triglycerides, uric acid, they can be compared for the two batches and they are within the normal range. But our attention is actually drawn on a difference between the batches with regard to serum cut-offs of HDL cholesterol (35.49±6.67 in patients with SA, as compared with 45.69±6.61 in the witness batch, p<0.001) and atherogenic index (5.54±1.19 in patients with SA, as compared with 3.91±0.93 in the witness batch, p<0.001), which situates patients with SA in a higher risk class, as compared to control subjects.

Biological parameters reflecting the inflammatory process recorded, regardless of the experimental batch, higher cut-offs as compared to the physiological limits, in accordance with the degree of activity of the disease.

The disease activity increase in patients with spondylitis was associated with the decrease of serum levels of lipids, but with a more atherogenic lipid profile, such as the decrease of HDL concentration twice more than the overall cholesterol.

Monitoring the disease activity parameters evolution after varied therapies (every 12 months) which patients benefited from, indicated their decrease tendency, the most significant one being recorded for the anti-TNF therapy. Thus, from the amelioration of the inflammatory condition interfering in certain areas with the lipid profile
might benefit patients with SA, decreasing the risk of atherosclerosis which is accelerated at this class of patients.

*Accelerated atherosclerosis reflection through the echographic objectivation of the atheroma plate from the level of the carotid arteries.*

The prominence through vascular echography of the atherosclerotic lesions thus formed, represented by the atheroma plate at the level of the carotid artery indicated a 21.43% incidence of patients with SA, as compared with the witness batch in which the incidence on the witness batch was 4.29%.

### PROFILE OF A PATIENT WITH PLEUROPULMONARY AFFECTATION

The pulmonary affectation was more frequently met in cases of patients with SA, the incidence of pulmonary abnormalities in cases of patients affected by the diseases being 37.14%, and in control subjects, their incidence was 10%.

The risk of pulmonary affectation in cases of patients with SA was in this study 5.32 times higher as compared to subjects who did not have SA (RR=5,32; IC95% 2,12 -13,33; p=0,004).

It was noticed a statistically significant correlation between the pleuro-pulmonary affectation and the patients’ age, the disease evolution average duration, the inflammatory condition, the disease progression, but there were no correlations with patients’ gender or the type of articular affectation. The pleuro-pulmonary affectation is associated with the increased incidence of the restrictive ventilatory dysfunction, pulmonary hypertension and at a certain segment of these, the effects on the right heart.
CONCLUSIONS

1. The frequency of cardiovascular affectation is significantly higher in patients with ankylosing spondylitis, regardless of the type of the analysed pathology. Variables such as the disorder evolution duration, the age, the inflammatory status and the diseases activity magnitude being significantly correlated with the risk of these extraskeletal onsets.

2. The aortic affectation is one of the most frequently met cardiovascular onsets. The risk of aorta dimensions increase is obviously more expressed in the case of patients with spondylitis, being higher for the ring region and in its vicinity. I have recorded a significant correlation between the aorta dimensions increase in patients from the batch with SA and the age of patients, the disease evolution duration, the inflammatory status and BASFI score, the most powerful impact being that of the disease evolution duration.

3. Aortic regurgitation was objectivised only for cases of patients with ankylosing spondylitis; thus there are significant correlations with the age of patients, the disease evolution duration, the VSH cut-offs, the serum average levels of hsCRP, BASDAI and BASFI scores.

4. The risk of the mitral insufficiency in cases of patients with ankylosing spondylitis was higher as compared to the cases of the witness batch and it was noticed a statistically significant correlation between the presence and the degree of mitral regurgitation and the age, the disease evolution duration and the BASFI functional score and an insignificant correlation tendency with definitory variables for the inflammation - VSH, hsCRP, as well as with the BASDAI score.

5. Patiens with SA show a higher risk to develop pulmonary hypertension, and the study results prove that the inflammatory status and the BASDAI scores have a statistically significant impact to define risk.

6. Diastolic function of the left ventricle alteration was confirmed in 1/3 of the cases of patients with SA, the risk being increased in those patients with inflammatory profile, advanced age, long duration of the
disease evolution and significant functional deterioration, quantified through the BASFI score.

7. The electrocardiographic abnormalities study identified a more increased incidence of driving disorders as compared to the witness batch, but statistically insignificantly, except the QT interval in cases of patients with SA, as compared to the control subjects.

8. The presence of the *endothelial dysfunction* as inaugural event in the atherosclerosis sequences, precociously detected through the quantification of the intima-media thickness at the level of the joint carotid arteries was more important in patients with SA and was significantly associated with the inflammatory status – especially with hs-CRP, age, disease evolution duration and disease severity.

9. The study results prove that patients with SA fall into a higher risk category because of the chronic inflammatory status and of a proatherogenic lipid profile, variables that mutually potentiate.

10. *Pulmonary affectation* was more commonly met in cases of patients with SA, the risk being significantly higher as compared to the control subjects, risk greatly caused by systemic affectation, extraskeletal, which is specific to the disease. Scattered interstitial infiltrations, bronchiecstasis and restrictive ventilatory dysfunction, entailing pulmonary hypertension, were statistically significant more frequently met in patients with SA. There is a statistically significant correlation between the pulmonary affectation and patients’ age, the disease evolution average duration, the inflammatory status, the advanced stages of the ankylosing spondylitis, without being noticed correlations with patients’ gender or the type of articular affectation.

The selection of most expressive variables for the risk of occurrence and progression of cardiovascular and pulmonary affectations over the course of the natural history of ankylosing spondylitis shall enable defining risk patterns as well as the creation of a risk matrix model— they are created as desiderata of the research extension, with the purpose of optimising both monitoring and therapeutic programs with prophylaxis and cure target.
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