Eur J Med Res (2007) 12: 573-581

Pathologic Alterations of the Heart and the Kidney in Patients with Ankylosing Spondylitis

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Abstract
Background: The occurrence of a variety of pathological lesions of the heart and kidneys have been described in patients with ankylosing spondylitis (AS). The frequency of these alterations and whether they are specific for AS has been discussed controversially.
Methods: Outpatients with AS were studied to determine the frequency of cardiac and renal alterations and to assess the associated clinical and demographic factors.
Results: A total of 77 patients with AS participated in the study (male 84.4%, mean age 48.3 ± 1.5 years, mean duration of disease 15.4 ± 1.2 years). Hypertension was present in 36.4% and diabetes mellitus in 13.0%. Impaired renal function (defined by a decrease in GFR) combined with markers of kidney damage suspective for chronic kidney disease were present in 3 patients (3.9%). Pathologic alterations of the heart were found in 25 patients (37.3%). Echocardiographic abnormalities were present in 20 patients (e.g. aortic and mitral insufficiency). Electrocardiographic abnormalities were present in 12 patients (e.g. atrioventricular, left and right branch block). Patients with cardiac abnormalities were older (54.2 ± 2.9 vs. 44.9 ± 1.7 years) and had a longer duration of disease (20.6 ± 2.1 vs. 13.9 ± 1.6 years) as compared to non-affected patients.
Conclusion: In our study, cardiac abnormalities were frequently seen in patients with AS, while renal disease was more rare and might be due to diseases not related to AS in most of patients. In contrast to cardiac involvement, it therefore appears questionable, that chronic kidney disease is part of the extraskeletal manifestations, or at least that AS has a high impact on renal integrity.

Key words: Ankylosing spondylitis, valve insufficiency, cardiac conduction disturbance, amyloidosis, IgA nephropathy

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease, which is strongly associated with HLA-B27. AS is mainly affecting the sacroiliac joints and the whole axial skeleton, but involvement of other organs, such as anterior uvea, kidney, lung and heart, has been described.

Cardiac disease is a complication of AS and other spondyloarthropathies with an estimated prevalence of 5-10% [1]. Cardiovascular alterations include dilated aortic ring, thickened and shortened aortic valves due to inflammation and consecutive fibrosis, which may also involve the mitral valve and impair the atrioventricular bundle causing partial and complete heart block. However, recent studies suggest that cardiovascular involvement in patients with AS is more common than was previously recognised and can been seen in up to 30% of AS patients by echocardiography, but cardiac alterations are usually subtle and subclinical [1-6]. The risk of occurrence of aortic insufficiency and cardiac conduction disturbance was reported to be associated with the duration of AS, the presence of HLA-B27 and peripheral joint involvement [1, 3, 5, 7]. But, epidemiological data on the prevalence of cardiac alterations are limited and their clinical characterization, relation to clinical features of AS, evolution and prognostic implications are unclear [1, 5-7].

Various types of renal disease, with or without impairment of renal function, have been described in patients with AS, usually presenting with proteinuria and microscopic hematuria, sometimes detected on routine analysis [8-10]. Renal involvement in AS is believed to be uncommon, but AS and related conditions, e.g. chronic use of nonsteroidal anti-inflammatory drugs (NSAID), have been associated with an increased risk for the development of renal amyloidosis, analgetic nephropathy, and IgA nephropathy (IgAN) in these patients [8-11]. Chronic renal failure in patients with AS has been reported to be attributable to amyloidosis in 62% and IgA nephropathy in 30 % of cases [8]. However, it has been discussed widely and controversially, whether kidney disease, especially IgAN, is secondary to AS and if there is an increased risk for chronic kidney disease in AS patients [9, 11-18].

The purpose of our study was to evaluate the frequency and severity of cardiac and renal abnormalities in AS patients and to examine the effect of AS and traditional risk factors on cardiac and renal disease in this population.

METHODS

PATIENTS

Patients with established diagnosis of AS (defined by New York clinical criteria and the European AS study Group classification criteria) seen at the Kerckhoff Outpatient clinic between the 1st of January 2001 and the 1st of July 2002 were asked to volunteer for this study [19, 20]. All the patients gave their informed consent according to the Declaration of Helsinki and approval for this study was given by the local ethical committee of the Justus-Liebig-University in Giessen. Patients with concomitant inflammatory bowel disease (terminal ileitis, ulcerative colitis), malnutrition or marasmus were excluded from the study. Patients were recruited after informed consent was obtained during a routine clinical visit. Information on parameters of ankylosing spondylitis, family history, medication, age, concomitant diseases or complicating conditions was assessed by history, a standardized questionnaire, a review of medical records and by physical examination. Vital signs obtained included blood pressure, height and body weight.

Patients were classified according to the degree of AS into the following subgroups (grade I to IV): symmetric sacroiliitis (grade I), sacroiliitis with one section of the spine involved (grade II), sacroiliitis plus two sections of the spine involved (grade III) and sacroiliitis plus three sections of the spine involved (grade IV).

Patients untreated for systemic hypertension showing diastolic blood pressure (DBP) values of ≥ 90 mmHg and/or systolic blood pressure (SBP) values of ≥ 140 mmHg in 2 or more office visits over at least 3 months prior to this study, as well as patients with treated hypertension irrespective of blood pressure values were regarded as hypertensive according to WHO/ISH guidelines definition [21].

Diabetes was defined as fasting blood glucose higher than 126 mg/dl in at least 2 office visits, when documented in the medical record or by the use of oral antidiabetics or insulin.

LABORATORY TESTS

Routine laboratory tests included electrolytes, blood glucose, ESR, CRP, serum creatinine, serum urea, immunglobulin A (IgA) and testing for autoimmune antibodies, such as ANA, ANCA, antiglomerular basement membrane antibodies, cryoglobulin, as well as lues-serology (ELISA and VDRL) and hepatitis B surface antigen. Middle-stream urine samples were analysed by urine-dipstick and phase-contrast microscopy of the sediment at two consecutive visits. Additionally, patients were asked to submit 24-hour urine collections for quantification of total proteinuria and estimation of glomerular filtration rate (GFR) by determination of 24-hour creatinine clearance. Proteinuria was defined as >150mg/day.

ELECTROCARDIOGRAPHY AND ECHOCARDIOGRAPHY

A standard 12-lead ECG was performed and evaluated in a blinded and separate fashion by two experienced investigators and eventually by consensus. Two-dimensional and Doppler transthoracic echocardiographic examinations were performed with subjects in the partial left decubitus position using an ultrasound machine (SONOS 5500, Philips) equipped with a 3 MHz imaging transducer. Alterations were defined according to general guidelines of the American Society of Echocardiography [22].

STATISTICAL METHODS

Demographic, clinical, and laboratory parameters were described for the patient cohort overall and for groups of patients defined by the presence or absence of cardiac and renal abnormalities. Continuous variables are expressed as mean ± standard error of the mean (SEM). Categorical and continuous variables were compared for univariate analysis between groups using the Kruskal-Wallis test and Chi-square test, respectively. All P values reported are two-sided, and all confidence intervals are 95% intervals. Statistical significance was defined as a $P \leq 0.05$.

RESULTS

DEMOGRAPHIC DATA AND CLINICAL CHARACTERISTICS OF THE STUDY POPULATION

A total of 77 patients with ankylosing spondylitis were enrolled in this study and included in the analysis. The majority were male (84.4%) and HLA-B27 positive (84.4%). No patient showed signs of peripheral joint involvement. Mean age was 48.3 ± 1.5 years and mean duration of diagnosed ankylosing spondylitis was 15.4 ± 1.2 years. Patients reported that onset of symptoms specific for ankylosing spondylitis started 20.3 ± 1.3 years prior to this study. All patients had received intermittent NSAID therapy during the last years. No patient was receiving glucocorticoid medication at the time of the study. One patient was receiving methotrexate as a disease-modifying medication. Systemic hypertension was present in 36.4% (28 of the total 77 patients) and diagnosis of hypertension was known since 9.1 ± 0.3 years. 10 subjects (13.0%) had diabetes mellitus with a mean duration of 7.0 ± 0.3 years. The demographic data and clinical characteristics are shown in Table 1.

RENAL ABNORMALITIES

Parameters of renal function and disorders are presented in Table 2. Three of the total 77 patients (3.9%) had chronic kidney disease with mild or moderate decrease of GFR according to the NKF K/DOQI guidelines [23].

In two patients chronic renal disease had been diagnosed prior to this study, but in none of these patients a renal biopsy had been performed to determine the underlying cause of impaired renal function. Both patients had a moderately decreased GFR between 40 and 60 ml/min per 1.73 m^2, a proteinuria of less than 1000mg/day and normal urine sediment. One patient had a mildly impaired GFR between 60 and 89 ml/min per 1.73 m^2 and a proteinuria of >1000

Table 1. Demographic data and clinical characteristics of the study cohort.

	Study population
Number	77
Mean age (years)	48.3±1.5
Gender [M/F (Ratio)]	65/12 (5.4)
BMI (kg/m^2)	26.8±0.6
HLA-B27 positive [n(%)]	65 (84.4%)
AS known since (years)	15.4±1.2
Typical symptoms of AS since (years)	20.3±1.3
Degree of AS [n(%)]	
Grade I	19 (24.7%)
Grade II	10 (13.0%)
Grade III	14 (14.2%)
Grade IV	34 (44.2%)
CRP (mg/dl)	1.63±0.19
ESR (mm/h)	20.4±2.1
Serum IgA (mg/dl)	312.4±17.8
Anti nuclear antibodies (ANA) positive [n(%)]	12 (15.6%)
Anti-neutrophil cytoplasmic antibodies (ANCA) positive [n(%)]	6 (7.8%)
Cryoglobulin positive [n(%)]	2 (2.6%)
Family history [n(%)]	
for hypertension	25 (32.5%)
for diabetes mellitus	15 (19.5%)
for renal disease	3 (3.9%)
Comorbidity [n(%)]	
Hypertension	28 (36.4%)
since (years)	9.1±0.3
Diabetes mellitus	10 (13.0%)
since (years)	7.0±2.3

Continuous data given as mean ± SEM.

Table 2. Renal abnormalities in AS.

	Study population
History of renal disease [n(%)]	2 (2.6%)
Serum creatinine [n(%)]	
< 1.2 mg/dl	74 (96.1%)
1.2 - 1.5 mg/dl	1 (1.3%)
> 1.5 mg/dl	2 (2.6%)
Creatinine clearance [n(%)]	
> 90 ml/min per 1.73 m^2	74 (96.1%)
60 - 89 ml/min per 1.73 m^2	1 (1.3%)
40 - 59 ml/min per 1.73 m^2	2 (2.6%)
Serum IgA >400mg/dl	18 (23.4%)
Hematuria [n(%)]	
Hematuria at study	4 (5.2%)
Self-reported history of hematuria	3 (3.9%)
History of urolithiasis	2 (2.6%)
Anticoagulation over-dosage	1 (1.3%)
Dysmorphic erthrocytes >10%	1 (1.3%)
Leucocyturia [n(%)]	7 (10.5%)
Concomitant urogenital infection	6 out of 7 (85.7%)
Proteinuria [n(%)]	10 (12.9%)
< 150 mg/24h [n(%)]	66 (85.7%)
150 - 500 mg/24h [n(%)]	7(9.1%)
500 - 1000 mg/24h [n(%)]	2 (2.6%)
> 1000 mg/24h [n(%)]	1 (1.3%)
Frequency of comorbidity (related to proteinuria) in proteinuric patients (n=10)	
No hypertension, no diabetes mellitus [n(%)]	2 (18.2%)
Hypertension [n(%)]	3 (27.3%)
Diabetes mellitus [n(%)]	1 (9.1%)
Hypertension + Diabetes mellitus [n(%)]	4 (36.4%)

mg/day, a normal urine sediment and concomitant diabetes mellitus and hypertension. Decrease of GFR was associated with concomitant hypertension ($P<0.05$) and an increase in age ($P<0.05$) in the study population.

Minor abnormalities of the kidney were observed in 14.3% of patients. Hematuria was observed in 4 patients (5.2%) by phase-contrast microscopy of the sediment. Within these patients, 2 patients had a medical history of urolithiasis with concomitant episodes of hematuria and in 1 patient hematuria was due to overdosage of oral anticoagulation. One patient with hematuria reported episodes of transient hematuria of unknown cause prior to study entry. In this patient additionally a proteinuria of 539 mg/day was found while serum creatinine as well as creatinine clearance were in normal range. Moreover, this patient was found to be the only patient with >10% of erythrocytes being dysmorphic in urine sediment.

IgA levels higher than the upper limit of normal controls (IgA >400mg/dl) were found in 18 patients (23.4%). Leucocyturia was present in 7 patients and in 6 cases was attributable to concomitant urogenital infection.

Proteinuria was present in 10 patients (12.9%) with a proteinuria of >1000mg/day in one and a proteinuria of <1000mg/day in 9 patients. Three of these patients had a decreased GFR, as described above. Within the proteinuric patients 5 had concomitant diabetes mellitus and 7 patients had concomitant systemic hypertension. Patients with proteinuria were more likely to be older than the average of the study population ($P<0.01$) and to have concomitant diabetes mellitus ($P<0.01$).

Ultrasound showed no pathological alterations of the urogenital tract besides a reduced kidney size (defined as <10 cm) and a reduced diameter of the renal cortex (defined as < 12 mm) in 2 patients.

No further significant differences were observed when comparing parameters of renal dysfunction and clinical and epidemiological data (data not shown).

Table 3. Cardiac abnormalities of AS.

Cardiac abnormalities [n(%)]	**25 (37.3%)**
Echocardiographic abnormalities [n(%)]	**20 (29.9%)**
Total numbers of abnormalities [n(%)]	
AI	9 (13.4%)
MI	7 (10.4%)
TI	8 (11.9%)
Left ventricular dysfunction	2 (3.0%)
Pericardial effusion	1 (1.5%)
Single or combined abnormalities [n(%)]	
AI alone	7 (10.4%)
MI alone	2 (3.0%)
TI alone	3 (4.5%)
Left ventricular dysfunction alone	2 (3.0%)
AI + MI + TI	2 (3.0%)
MI + TI	3 (4.5%)
TI + Pericardial effusion	1 (1.5%)
Electrocardiographic abnormalities	**12 (17.9%)**
AV-block	5 (7.5%)
Richt bundle branch block	4 (6.0%)
Left bundle branch block	2 (3.0%)
Sinus Bradycardia	1 (1.5%)
Echocardiographic + electrocardiographic abnormalities	**7 (10.4%)**

Cardiac Abnormalities

Out of the total 77 patients 67 completed the work-up on cardiac alterations. Within these patients 25 (37.3%) had cardiac abnormalities. Echocardiographic abnormalities were present in 20 patients (29.9%) and electrocardiographic abnormalities were present in 12 patients (17.9%). Abnormalities observed included anatomical alterations such as aortic (AI), mitral (MI) and tricuspid insufficiency (TI), systolic left ventricular dysfunction, pericardial effusion and conduction disturbances such as atrioventricular, left and right branch block as well as sinus bradycardia. These findings are summarized in Table 3.

To investigate possible associations of cardiac manifestations with clinical features of AS, four groups of patients were defined: patients with any type of cardiac alterations (n=25 patients), the subgroup of patients with echocardiographic alterations (n=20 patients) and the subgroup of patients with electrocardiographic alterations (n=12 patients) and compared to the control group of AS patients without these cardiac abnormalities.

When comparing patients with cardiac abnormalities to those without in terms of clinical parameters and demographic data both groups were similar with few exceptions (Table 4). Significant differences observed included, that patients with cardiac abnormalities were older (54.2 ± 2.9 vs. 44.9 ± 1.7 years, P <0.01) and had a longer duration of diagnosed AS (20.6 ± 2.1 vs. 13.9 ± 1.6 years, P<0.02).

Those differences were also observed, when comparing those patients with echocardiographic abnormalities separately to those without (for age 54.5 ± 3.4 vs. 45.8 ± 1.7 years, p<0.02; for duration of diagnosed AS 21.8 ± 2.3 vs. 14.1 ± 2.0 years, P<0.02) (Table 5). In contrast to these findings, no significant differences were observed between patients with electrocardiographic abnormalities and those without in terms of age and duration of AS, but patients with electrocar-

Table 4. Comparison of demographic and clinical data between patients with cardiac and without cardiac abnormalities.

	Cardiac abnormalities	**No cardiac abnormalities**	**P value**
Number (%of study population)	25 (37.3.%)	42 (62.7%)	
Mean age (years)	54.2 ± 2.9	44.9 ± 1.7	P<0.01
Male [n(%)]	24 (96.0%)	33 (78.6%)	P = NS
HLA-B27 positive [n(%)]	20 (80.0%)	35 (83.3%)	P = NS
AS known since (years)	20.6 ± 2.1	13.9 ± 1.6	P<0.02
Typical symptoms of AS since (years)	25.8 ± 2.4	18.5 ± 1.6	P<0.02
Degree of AS [n(%)]			P = NS
Grade I	6 (24.0%)	10 (23.8%)	
Grade II	6 (24.0%)	3 (7.1%)	
Grade III	4 (16%)	7 (16.7%)	
Grade IV	9 (36.0%)	22 (52.4%)	
CRP (mg/dl)	2.27 ± 0.46	1.20 ± 0.96	P = NS
ESR (mm/h)	28.4 ± 4.6	15.0 ± 1.9	P<0.05
Serum IgA (mg/dl)	312 ± 32	293 ± 25	P = NS
BMI (kg/m^2)	26.8 ± 0.8	27.2 ± 0.8	P = NS
Hypertension	13 (52.0%)	13 (31.0%)	P = NS

Continuous data given as mean ± SEM; NS = not significant.

Table 5. Comparison between patients with and without echocardiographic abnormalities.

	Echocardiographic abnormalities	**No echocardiographic abnormalities**	**P value**
Number (%of study population)	20 (29.2.%)	47 (70.8%)	
Mean age (years)	54.6 ± 3.4	45.8 ± 1.7	P<0.02
Male [n(%)]	19 (95.0%)	38 (80.9%)	P = NS
HLA-B27 positive [n(%)]	15 (75.0%)	35 (74.5%)	P = NS
AS known since (years)	21.8 ± 2.3	14.1 ± 2.0	P<0.02
Typical symptoms of AS since (years)	26.4 ± 2.5	19.1 ± 1.6	P<0.03
Degree of AS [n(%)]			
Grade I	5 (25.0%)	11 (23.4%)	
Grade II	4 (20.0%)	5 (10.6%)	
Grade III	3 (15%)	8 (17.0%)	
Grade IV	8 (40.0%)	23 (49.0%)	
CRP (mg/dl)	1.99 ± 0.50	1.44 ± 0.20	P = NS
ESR (mm/h)	26.7 ± 5.5	17.2 ± 2.0	P = NS
Serum IgA (mg/dl)	312 ± 41	296 ± 23	P = NS
BMI (kg/m^2)	26.5 ± 0.9	27.3 ± 0.8	P = NS
Hypertension	13 (52.0%)	13 (31.0%)	P = NS

Continuous data given as mean ± SEM; NS = not significant.

Table 6. Comparison between patients with and without electrocardiographic abnormalities.

	Electrocardiographic abnormalities	**No electrocardiographic abnormalities**	**P value**
Number (%of study population)	12 (17.9%)	55 (82.1%)	
Mean age (years)	53.5 ± 4.7	47.2 ± 1.7	P = NS
Male [n(%)]	12 (100.0%)	45 (81.8%)	P = NS
HLA-B27 positive [n(%)]	10 (83.3%)	45 (81.8%)	P = NS
AS known since (years)	18.1 ± 3.1	16.1 ± 1.5	P = NS
Typical symptoms of AS since (years)	23.8 ± 3.8	20.7 ± 1.5	P = NS
Degree of AS [n(%)]			
Grade I	2 (16.7%)	14 (25.5%)	
Grade II	2 (16.7%)	7 (12.7%)	
Grade III	2 (16.7%)	9 (16.4%)	
Grade IV	6 (50.0%)	25 (45.5%)	
CRP (mg/dl)	3.28 ± 0.84	1.23 ± 0.13	P<0.05
ESR (mm/h)	32.0 ± 6.5	17.4 ± 2.2	P<0.02
Serum IgA (mg/dl)	298 ± 49	300 ± 22	P = NS
BMI (kg/m^2)	27.3 ± 1.3	27.0 ± 0.6	P = NS
Hypertension	7 (58.3%)	19 (34.6%)	P = NS

Continuous data given as mean ± SEM; NS = not significant

diographic abnormalities had higher ESR (32.0 ± 6.5 vs. 17.4 ± 2.2 mm/h, P<0.05) and CRP (3.28 ± 0.84 vs. 1.23±0.13 mg/dl, P<0.05) than those without (Table 6).

Discussion

A variety of pathological lesions of the heart and kidneys have been described in the setting of ankylosing spondylitis (AS). The frequency of these alterations and whether they are specific for AS has been discussed controversially.

In our present study, we found a high frequency of cardiac abnormalities by assessing electrocardiography and echocardiography in patients with AS (37.3%). Twenty patients (29.9%) had echocardiographic and 12 patients (17.9%) had electrocardiographic abnormalities. Within these patients combined electrocardiographic and echocardiographic alterations were present in 7 patients (10.4%). In comparison to cardiac abnormalities renal disorders were observed much less frequent in our study cohort. Three patients (3.9%) had chronic kidney disease with mild or moderate decreased GFR and proteinuria. Additionally, 6 patients (7.8%) had isolated proteinuria, 7 patients (11.9%) had isolated hematuria, 1 patient had hematuria and proteinuria

and 1 patient had sterile leucocyturia as markers suspective for occult nephropathy, but no further sign of impairment of renal function or loss of GFR.

Cardiac Abnormalities

Four different anatomic sites of the heart might be involved in AS: the aortic route, the conduction system, the myocardium and the pericardium [1,3]. Fibrotic changes of the aortic root and subaortic structures leading to aortic valve disease and consecutive insufficiency have been described in AS. Prevalence of aortic valve disease in AS has been estimated to range between 4% in early and 10 % in later disease stages [1, 24, 25]. Inflammation and fibrosis may also affect the mitral valve and mitral regurgitation has also been described in patients with AS, but seem to be much less common [3, 7]. Tricuspid regurgitation has been reported only in individual cases [7]. However, several more recent echocardiographic studies have demonstrated a high frequency of subclinical changes of the aortic root and valve in AS patients in terms of changes in echogenicity, suggesting that cardiovascular involvement is more common than previously recognised with an estimated prevalence ranging between 8 and 31% [4-7, 26].

Conduction disturbance in patients with AS has been linked to fibrotic changes of the membranous part of the intraventricular septum is most often located in the atrioventricular node [2]. In individual cases bradycardia due to sinus node dysfunction has also been reported [3]. Additional studies demonstrated a greater QT dispersion and frequency of ventricular extrasystoles in AS patients by assessing 24-hour Holter examinations, but data have been discussed controversially [27, 28]. Prevalence of conduction abnormalities is estimated to range between 3% in early AS and 9% in later disease stages [24, 25]. However, epidemiological data on prevalence of cardiac alterations are limited and their clinical characterization, relation to clinical features of AS, evolution and prognostic implications are unclear [1, 5-7].

In our study cohort, we found cardiac abnormalities by assessing electrocardiography and echocardiography in 25 patients (37.3%) with AS. Echocardiographic alterations were present in 20 patients (29.9%) and electrocardiographic alterations in 12 patients (17.9%). Our results, in terms of frequency of valve regurgitation and conduction disturbance are similar to those observed in a retrospective study, but abundantly higher than in a recently published study [29, 30]. This discrepancy might be due to differences in mean age and duration of disease in the study populations, as it has been postulated that cardiac disease in AS is associated with patients' age and duration of AS, which is confirmed by our observations, as cardiac abnormalities were associated with a higher age and a longer duration of AS in our study population ($P<0.01$ and $P<0.02$, respectively) [1, 5, 30].

When comparing subgroups of patients with different types cardiac alterations separately to those patients without cardiac alterations, we found that patients with echocardiographic abnormalities were significantly older and had a longer duration of AS (both $P<0.02$), while no such differences were observed in AS patients with electrocardiographic alterations. Interestingly, patients with electrocardiographic alterations had significant higher CRP and ESR than those without ($P<0.05$ and $P<0.02$, respectively).

Conduction system disorders seem to occur intermittently in patients with AS [27, 31, 32]. It has been speculated, that the intermittent nature of conduction disturbance might be attributable to reversible cardiac inflammatory processes rather than fibrosis or to changes in the autonomic nervous system related to inflammatory activity [3, 33]. Moreover, it has been demonstrated that, conduction disturbances usually appear prior to the advent of valve incompetence in the majority of cases [34,35]. Our finding, that electrocardiographic alterations are associated with an elevated CRP and ESR but not with age and duration of AS, might therefore argue in favour to the hypothesis, that acute inflammatory processes but not to chronic alterations such as fibrosis is responsible for conduction disturbances in AS.

In patients with permanently implanted pacemakers prevalence of AS was found to be significantly higher as to be expected in the general population and an association between the development of lone aortic incompetence, heart block and HLA-B27 has been widely discussed [3, 32]. We were unable to establish a significant association between any type of cardiac abnormality and HLA-B27 in our study cohort, but numbers of HLA-B27 negative patients might have been too small in our cohort.

Renal Involvement

Prevalence of renal abnormalities in AS patients has been estimated to be lower than 10% [8]. It has been speculated, that renal amyloidosis, IgAN and analgetic nephropathy occur in a higher frequency in AS patients than expected in the general population, but only limited epidemiological data on that prevalence do exist [9, 11, 13-18].

An estimated prevalence of secondary amyloidosis (AA type) of 3 and 16% has been reported in patients with AS, but amyloidosis is nowadays more rarely observed in AS patients, which might be attributable to the more widespread use of NSAIDs and other drugs for better control of chronic inflammation [25, 36, 37]. Moreover, in most cases amyloid deposits in patients seem to have little clinical significance and represent an occasional finding in a routine fat or rectal biopsy, as renal amyloidosis with progression to chronic renal failure has only been reported in individual cases [10, 38]. However, amyloidosis usually is a late complication of AS (duration of disease > 30 years) and is often remained undiagnosed until late in its course because of its slow evolution and relative rarity [10, 25]. IgA nephropathy is thought to be the most common type of glomerulonephritis in AS and an association of ankylosing spondylitis and IgAN has been reported in few studies and in several individual cases, but these findings have been discussed controversially [8, 9, 11-18]. Common patterns of both diseases include elevated levels of IgA and a high fre-

quency of hematuria [9, 11, 13, 39, 40]. Additionally, IgAN has been speculated to be related to HLA-B27 and IgA levels are higher in HLA-B27 positive as compared to HLA-B27 negative patients with AS [41]. Moreover, downregulation of Fc α-receptors have been reported in both IgA nephropathy and ankylosing spondylitis what can therefore present a common pathogenetic pathway [39]. Renal disease in AS patients can also result from chronic NSAID use, leading to tubulointerstitial nephritis or a decrease in medullary blood flow in patients with pre-existing renal damage [42].

In our present study, three patients (3.9%) had chronic kidney disease with mild or moderate decrease of GFR and proteinuria. Minor abnormalities of the kidney were observed in 14.3% of patients, as 6 patients (7.8%) had isolated proteinuria, 3 patients (3.9%) had isolated hematuria, 1 patient had combined hematuria and proteinuria and 1 had patient sterile leucocyturia, but no further sign of impairment of renal function or loss of GFR.

We did not perform any renal biopsy in our patients. While most patients with renal abnormalities did not meet criteria for indication of renal biopsy, three patients had chronic kidney disease with mild or moderate decreased GFR and proteinuria of unknown cause. However, in one case kidney disease is most likely due to diabetic nephropathy as this patient had a long history of insulin-dependent diabetes with poor control of blood glucose levels and presented with a mild decrease of GFR and proteinuria but no parameters indicative for glomerulonephritis. The other two patients had mild proteinuria, a moderate decrease of GFR, but normal urine sediment. In one patient chronic kidney disease was already known for 18 years with almost stable impairment of renal function over the time course. In the other patient chronic renal insufficiency had developed after unilateral nephrectomy. Clinically, amyloid nephropathy manifests itself with unselective proteinuria, progressing to nephrotic syndrome and renal insufficiency. Analgetic nephropathy presents with nephritic low range proteinuria in association with renal insufficiency, sterile leucocyturia in urine analysis. It therefore, appears unlikely that amyloidosis or analgetic nephropathy are the underlying cause of chronic renal disease in these patients. Episodes of hematuria have never been reported in these patients, but this does not completely rule out, that renal impairment in these patients is due to IgA nephropathy.

Our findings in terms of frequency of renal abnormalities such as proteinuria, hematuria and elevated IgA levels are similar to those described by others demonstrating a prevalence of unexplained hematuria and proteinuria in up to 10% of AS patients [9, 11, 13, 25, 39, 40]. Because of these findings, it has been speculated, that the incidence of IgAN is higher than in the general population as IgAN might remain unrecognised in most patients [8, 9, 11, 13, 43]. However, the true prevalence of IgAN in AS patients remains unknown and estimations of prevalence of IgAN varies widely between 0.25-5% of patients with AS [8, 13-18]. In contrast, to these observations other authors did not find an increased risk for IgAN in patients with AS [12, 15-18]. However in our study, hematuria may be attributable to urolithiasis in 2 patients and to oral anticoagulation in one patient. Only 1 patient had dysmorphic erythrocytes in urine sediment, indicative for hematuria of glomerular origin. Proteinuria was present in 10 patients (12.9%), but most patients had only mild proteinuria of less than 500 mg/day. Eight of these patients had concomitant diabetes mellitus and/or hypertension, diseases known to cause proteinuria. Accordingly, patients with proteinuria were found to be older than the average of the study population and more likely to have concomitant diabetes mellitus. Additionally, we observed no significant correlation between parameters of renal dysfunction and clinical and epidemiological data of AS, which has also been reported by other groups [9, 12]. Moreover, IgAN is the most common type of glomerulonephritis (15-40%) and time course of IgA nephropathy is varying widely ranging from spontaneous remission (approximately 23%) to chronic renal failure (15-30%). It is therefore not surprising, that IgAN is often a chance finding and detected more frequently if patients with minor urinary abnormalities undergo biopsy, as generally renal biopsy is not recommended when presented only with isolated hematuria or mild proteinuria [44, 45]. Hence, the majority of affected persons probably never come to medical attention, since in autopsies a prevalence of 1-4% of the population has been reported [46, 47]. This prevalence of IgAN is similar to those observed in patients with AS. As the majority of cases with coincidence of IgAN and AS described in the literature had only minor renal alterations, this may suggest, that IgAN is not more frequent in patients with AS than in the general population [16-18]. Moreover, elevated IgA levels were found in only 33 to 50 % of patients with IgA nephropathy and IgA levels were not correlated with intensity and time course of disease [44]. Additionally, a proteinuria of less than 1000mg/day and only intermittent hematuria were associated with a good clinical prognosis [45]. In regards to these findings, it appears questionable that the minor renal abnormalities observed are secondary to AS in most of our patients.

Conclusion

The process of cardiac involvement in AS can produce varying disease profiles and has a high variability in its time course and intensity reaching from spontaneous remission up to clinically important cardiac disease and may be seen in AS patients even in the absence of clinical cardiac manifestations. Patient older and with longer duration of disease have a higher frequency of cardiac alterations, but especially conduction disturbance seems to be associated with acute inflammatory processes and might therefore occur more frequently in younger patients as well.

Renal abnormalities are frequently seen in patients with AS. Abnormalities observed vary, but are mild and unspecific in most cases. Moderate or severe impairment of renal function occurs only in a minority of patients. From our data it appears questionable, whether AS has a high impact on renal function, resulting in an elevated risk of end stage renal disease in these patients as compared to the general population.

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Received: June 18, 2007 / Accepted: July 24, 2007

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