Ankylosing spondylitis – Cardiac manifestations

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ABSTRACT

There is a definite association of heart disease with ankylosing spondylitis (AS). The magnitude of this relationship is less clear. Three types of inflammatory affections can be differentiated: 1. aortitis and aortic insufficiency with the possible necessity of cardiac surgery, 2. conduction disturbances of the atrioventricular node with a probable subsequent indication for a pacemaker and 3. myocardial involvement with a possible compromise of left ventricular function. There seems to be an HLA B27-associated cardiac syndrome consisting of aortic root disease and conduction abnormalities. Patients can be recognized at pre-clinical stages. Prospective studies have not been performed. HLA B27-related heart disease does not seem to be associated with increased mortality.

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease which is strongly associated with the HLA class I molecule HLA B27. AS mainly affecting the sacroiliac joints and the whole axial skeleton causes inflammatory back pain in many young patients. Involvement of other organs such as the anterior uvea is well known in AS. Furthermore, manifestations of this systemic disease have also been reported in the kidney, the lung and the heart of AS patients (1-3). This review focusses on the cardiac manifestations of AS. There are four different anatomic sites in the heart which can possibly be involved in AS: the region around the aortic root (4), the conduction system (5), the myocardium (6) and, rarely, the pericardium (7). As of July 1st, 204 citations on 'AS and heart' were identified in PubMed.

1. Involvement of the aorta and related structures in ankylosing spondylitis

Anatomically, there is evidence of involvement of the aorta ascendens, mainly the aortic root, but also subaortic structures such as the membraneous part of the interventricular septum leading to conduction disturbancies (see below) and the basis of the anterior mitral leaflet in AS leading to minor mitral regurgitation (8). The event of aortitis needs to be seen in connection with aortic valve disease due to the close proximity of these structures. This includes dilatation of the aortic ring and valvular changes.

Aortitis

The histopathological features of the inflammation in the aorta of 8 AS patients have been reported by Bulkley and Roberts in 1973 (8). Focal destruction of muscular and elastic structures of the media, thickening of intima and adventitia and obliterative vessel disease, similar to syphilitic aortitis, have been described (8). Today, the diagnosis of aortitis in AS is a rather rare event but the exact prevalence is not known.

Aortic valve disease

The typical valvular changes in AS have been described early as fibrotic, thickened, and retracted cusps with rolled edges (8). These changes typically lead to aortic insufficiency (AI) over time. The prevalence of aortic valve disease in AS has been calculated at 4% of 'early' AS (defined as disease duration < 15 years) and 10% in later disease stages, defined as disease duration > 30 years (9). However, there are no good epidemiological data on that prevalence. Nevertheless, we have identified some studies which seem to be worth mentioning.

In a retrospective study (10), 40 AS patients were assessed for extraspinal manifestations of the disease. Cardiovascular complications were found in 17 patients (42.5%): 5 (12.5%) had aortic insufficiency, 3 (7.5%) had atrioventricular (AV) block and 5 (12.5%) had bundle branch block. Cardiovascular complications were more common

in patients with longer disease duration. Ischemic heart disease was found in 17.5% of the cases.

However, in general, it has to be stated that the overall prevalence of ischemic heart disease in AS is not known. There is no evidence to date that there is an increased morbidity or mortality due to coronary artery disease in AS as has been reported in rheumatoid arthritis (11).

Subaortic fibrosis
The terminus 'subaortic bump' refers to fibrosis of the basis of the anterior mitral leaflet in AS which has been described as a specific indicator of affection of subaortic structures in AS (8, 12).

Subaortic fibrous ridging or marked leaflet thickening was noted in 11 of 36 patients with spondyloarthritis (SpA) but not in an age-matched control group of 29 men (13). In this study, two-dimensional transthoracic echocardiography (TTE) was performed in a group of 36 SpA patients (25 AS, 9 patients with Reiter's syndrome, and 2 patients with inflammatory bowel disease and spondylitis), in which no patient had clinical or laboratory evidence of aortic regurgitation or heart block.The subgroup of patients with subaortic fibrous ridging or leaflet thickening (11 patients) had significantly longer disease duration (28.1 versus 17.7 years) and higher incidence of aortic root echo-density (82 versus 36 percent) than the remaining patients. The authors concluded that a significant portion of SpA patients have aortic root involvement prior to the clinical onset of aortic regurgitation (13).

In another non-invasive study using TTE with 35 AS patients without clinically apparent cardiac involvement basically no abnormally increased aortic dimensions suggestive of aortic dilatation were found (14). However, two patients had aortic dimensions greater than 4.2 cm at the valve (normal 4.0 cm). Also, 6 patients had discrete areas of increased bright echoes below the left or noncoronary cusps suggestive of a subaortic "bump" and two of these patients had increased aortic cusp echoes suggestive of thickening or fibrosis, or both. The authors of this study concluded that aortic root changes suggestive of inflammation, fibrosis, or both, do occur in asymptomatic AS patients.

Transesophageal echocardiography (TEE) allows a closer view of the aortic root and subvalvular structures. Using this technique (12), aortic root and valve disease were even more common in 44 AS patients (82%) as compared with 30 age- and gender-matched healthy controls (27%; p < 0.001). Aortic root thickening, increased stiffness and dilatation were seen in 61%, 61% and 25% of patients, respectively. Valve thickening (41% for the aortic and 34% for the mitral valve) manifested predominantly (74%) as nodularities of the aortic cusps and basal thickening of the anterior mitral leaflet, forming the characteristic subaortic bump. Valve regurgitation was seen in almost half of patients, and 40% had moderate lesions. Except for the duration of AS, aortic root disease and valve disease were unrelated to the activity, severity or therapy of AS. Importantly, during follow-up of 25 patients after a mean of 39 ± 10 months, new aortic root or valve abnormalities developed in up to 24% and existing valve regurgitation worsened significantly in 12%, while in 20% abnormalities resolved. Of note, 20% of the patients were reported to have developed heart failure, undergone valve replacement, have had a stroke or have died, while only 3% of the controls had such severe outcomes. The authors concluded that aortic root and valve disease are very common in AS patients, are unrelated to clinical features of the disease, can resolve or progress over time and are associated with clinically important cardiovascular morbidity.

The lack of sensitivity of standard cardiologic techniques such as clinical examination, electrocardiography, and TTE to detect cardiac abnormalities was also stressed in another study using TEE in 29 male AS patients and 13 controls (15). The posterior aortic wall was found to be thicker and subjectively more echogenic than the anterior wall in 17 AS patients compared to controls. In 8/9 AS patients studied with TEE, the subaortic structures were thickened and/or of increased echogenicity, extending into the membranous septum. It was concluded, that the use of TEE may allow earlier diagnosis of cardiac involvement in AS.

Aortic insufficiency, spondylo-arthritides and HLA B27
The prevalence of SpA was examined in 100 consecutive patients with lone AI (16). Of interest, 4 patients were found to have AS and 3 had Reiter's syndrome. Six of these seven HLA-B27-positive patients had cardiac conduction abnormalities with 4 requiring permanent pacemaker insertion. All 7 patients were HLA-B27-positive. In contrast, out of 89 patients with no evidence of spondylitis only 5 had the antigen (5.6%). The authors concluded that SpA are associated with lone AI and that HLA-B27 is not associated with lone AI in the absence of spondylitis. Taken together, the prevalence of SpA was found to be clearly increased in patients with lone AI.

Bergfeldt studied a group of 91 patients with lone aortic regurgitation by HLA typing, clinical and roentgenologic examination (17). Of interest, in 15 to 20 percent of these patients an HLA-B27-associated inflammatory disease process was found to be the possible underlying cause, while there was no significant association between lone aortic regurgitation and HLA B27 alone. Furthermore, HLA-B27 was found in 88% of the male patients with the combination of aortic regurgitation and severe conduction system abnormalities. Bergfeldt thus proposed that this combination is a novel HLA B27-associated non-spinal cardiac syndrome among the HLA B27-related inflammatory immune-mediated diseases.

2. Conduction abnormalities in ankylosing spondylitis
Localisation
The first indication of an association of conduction abnormalities with HLA B27 and AS was noted by Weed in 1966 (18). Later, the relation between conduction disturbances and the affection of the membraneous part of the

interventricular septum was recognized (8). Occasionaly, an extension of the aortitis onto the interventricular septum results in 2nd and 3rd degree AV and fascicular blocks (12). The anatomic site of the AV conduction problems in AS is mainly localized in the suprahisian region (5) as reported by Bergfeldt in an electrophysiological study of 12 patients with spontaneous complete heart block and HLA B27 associated disease (8 with AS). Of these, 10 had suprahisian 2nd or 3rd degree AV block and 3 patients also had sinus node malfunction and 6 had fascicular or bundle branch block. Of note, in HLA B27-positive patients, the 3rd degree (complete) AV block is located within the AV node in 95% rather than the expected 20% of cases (3).

Prevalence, association with spondyloarthritides and HLA B27 association
The prevalence of conduction abnormalities is reported to be 3% in early AS (defined as disease duration <15 years) and 9% in later disease stages (defined as disease duration > 30 years) (9). However, there are no good epidemiological data on that prevalence. Nevertheless, we have identified some studies which seem to be worth mentioning.
In a population of 223 men with permanently implanted pacemakers, the prevalence of AS was assessed by screening pelvic radiographs (19). Sacroiliitis was found in 19 men (8.5%), 15 of whom fulfilled the diagnostic criteria for AS (6.7%). These prevalence rates differ significantly (p < 0.01) from the frequencies found in general Caucasian populations of 1 to 2 and 0.1 to 0.5 percent, respectively (19). Thus, a 15-fold increase in the prevalence of AS in this population with permanent cardiac pacemakers was calculated.
In an extension of this study (20) Bergfeldt reported on 28 patients (12.6% (95% CI:8.2– 17%), who fulfilled SpA criteria, including 15 with AS (see above), 85% being B27-positive. Of interest, a diagnosis of SpA had previously been made in less than 50% of the patients. Taken together, patients with severe bradyarrhythmias associated with SpA were found to constitute a

large proportion of this population of men with permanent pacemakers in which a high frequency of aortic regurgitation and all kinds of bradyarrhythmias was reported: 20 SpA patients had complete heart block (71%), which, in the majority of cases, occurred intermittently, but otherwise without distinguishing features.
In another study of Bergfeldt (21), the frequency of B27 was determined in 83 permanently paced men with complete heart block, in whom presence of radiological or clinical signs of a B27-associated rheumatic disease had been excluded and 84 healthy subjects. HLA B27 was found in 17% of the patients but in only 6% of the controls (p = 0.017). This significant difference needs to be discussed in the context of other scandinavian studies in which higher frequencies of HLA B27 were reported (22). Nevertheless, Bergfeldt concluded that the development of heart block might be HLA B27-associated in a subgroup of patients.
The prevalence of SpA was also assessed in a Dutch study (23) on 35 patients with a pacemaker and heart block of unknown cause, selected from a total group of 350 men with pacemakers who were still alive at the time of the study. One of these 35 male patients had AS and another 2 patients had an asymptomatic sacroiliitis, but all three were HLA-B27 negative. In some contrast, HLA-B27 was present in 5 (14%) pacemaker patients - a significantly higher prevalence than in healthy controls (17/292 = 6%). The authors concluded that for the pathogenesis of heart block there must be more critical factors than HLA B27 which cause the disease.
In his latest review from 1997 (4), Bergfeldt underlined that the frequency of HLA-B27 among men but not women with implanted pacemakers is significantly increased as compared to the general population. Similar to the established prevalence of HLA B27 in AS and Reiter's syndrome, a cardiac syndrome that consists of severe conduction system abnormalities plus aortic regurgitation associated with HLA-B27 was found to be present in 67% to 88% of the patients with both of these

clinical findings. Both cardiac conduction abnormalities and aortic regurgitation occur in patients with various HLA-B27-related extracardiac disorders, regardless of the severity of the latter. The mortality among pacemaker patients in comparison to the general population was also studied by Bergfeldt (24), with comparisons made between patients with and without HLA B27 and associated disorders. No influence on mortality associated with HLA B27 or with HLA B27-associated rheumatic disorders was found in this study.

Other studies on electrocardiographic 'abnormalities' in ankylosing spondylitis
Ambulatory 24-hour Holter monitoring revealed electrocardiographic (ECG) 'abnormalities' in 12 out of 48 HLA B27-positive AS patients in a study (25) in which the frequency of AV blocks and atrial tachycardia was reported to be higher than in healthy controls. In another ECG- based study (26), records of 99 AS patients and 132 of their adult first degree relatives were obtained. The distribution of P-R intervals were similar in the groups, only 4 cases of 1st degree AV block were detected, one of them had aortic valve insufficiency. One single case of pronounced conduction delay (P-R interval 0.42 sec) was recorded in an otherwise healthy HLA B27-positive relative. The authors concluded that cardiac conduction disturbance was not more frequent in AS patients or in their relatives.
To assess the repolarization heterogeneity in AS, the QT dispersion (QTd) was examined by 24-h Holter monitoring in 88 AS patients and controls (27). The QTd was found to be greater in AS patients (p < 0.0001). This was correlated to disease duration (r = 0.60, p < 0.001) and to the frequency of ventricular extrasystoles (r = 0.33, P: < 0.01). Early application of this technique might identify AS patients at risk for myocardial involvement. However, these findings need to be confirmed.

Involvement of the autonomous nervous system in ankylosing spondylitis
The involvement of the autonomic ner-

vous system (ANS) was analysed by power spectral analysis of heart rate variability in AS patients. While one group (28) could not demonstrate any evidence of ANS involvement in AS (n = 94), another group (29) reported some changes in ANS function in 18 AS patients: a decreased parasympathetic activity, as evidenced by higher HR and lower baroreflex slope. Since these deviances were mainly observed in patients with active disease the authors concluded that these changes were more probably realted to the inflammatory process than to the disease itself.

3. Left ventricular dysfunction in ankylosing spondylitis

Cardiac function was investigated in 74 male AS patients (age 21-65 years) who had no cardiorespiratory symptoms or known abnormalities of heart or lungs (6). Chest radiographs and standard electrocardiograms were normal in 73 subjects. In echocardiographs of 30 men, left atrial size and left ventricular cavity size and wall thickness were normal. Minor abnormalities in the valve roots were present in 3 older men. Early diastolic abnormalities of the left ventricle were demonstrated in 16 of 30 subjects. This finding was confirmed by repetition of the echocardiography one year later in 15 subjects and by comparison of 11 probands with their healthy brothers. In addition, myocardial tissue obtained at necropsy from 28 AS patients without ischaemic or valvular heart disease or hypertension was studied. A mild, diffuse increase of interstitial connective tissue was seen but there was no inflammatory change or amyloid. Computerised image analysis showed 30.7% interstitial reticulin compared with 17.7% in age/sex matched controls (p < 0.0001). Brewerton concluded that 53% of the AS patients had evidence of diastolic dysfunction and that most AS patients had a mild increase of the interstitial connective tissue in the myocardium (6).

In a study on 51 male patients the cardiac abnormalities in juvenile onset AS (JOAS, n=20) and adult onset AS (AOAS, n = 31) were assessed by 2-dimensional TTE and compared to 20 healthy controls (30). An unusual finding reported was that 90% of the JOAS but only 51% of AOAS patients were B27-positive (p = 0.005). The disease duration was similar: 15-20 years. There was a strikingly higher frequency of cardiomyopathy in AOAS (32.2%) and JOAS (25%) than in the controls (0%), (p = 0.01).

In another study (31), the prevalence of both systolic and diastolic left ventricular (LV) dysfunction and other cardiac abnormalities in AS patients without clinical cardiac manifestations was assessed (n = 59 patients; 49 men, mean age 42; mean disease duration 17 years). By echocardiography, abnormal LV diastolic function was detected in 12 patients (20%). Prolonged isovolumic relaxation time, prolonged deceleration time, reduced rate of descent of flow velocity in early diastole (EF slope) and reversal of the early and late peak transmitral diastolic flow velocities (E/A ratio) were noted in 9 patients. Mild aortic regurgitation and mitral regurgitation was seen in 1 and 3 patients, respectively. There was no correlation between the presence of LV diastolic dysfunction and age, disease severity, disease duration, or the presence of extraarticular manifestations.

The cardiac function at rest was assessed in 21 AS patients and 20 age, sex, height, and weight-matched healthy controls using echocardiography, and, in addition, at rest and during supine bicycle exercise, using radionuclide angiography in the left anterior oblique position following equilibration with 740 MBq of technetium-99. No echocardiographic differences between patients and controls were detected. However, the global nuclide left ventricular function did show differences: the peak filling rate during exercise and also the time to reach peak filling during exercise was significantly lower in AS patients. Importantly, most differences detected in AS patients were related to the diastolic function (32).

Amyloidosis of the kidney occurs in a minority of AS patients while cardiac amyloidosis is even rarer (1, 33). Amyloidosis of the kidney was found to be associated with mortality in AS (34). Echocardiographic findings in seven patients with infiltrative cardiomyopathy due to amyloid were reported by Child et al. (35); one of these had AS. The basic echocardiographic findings in infiltrative cardiomyopathy due to amyloid were (i) symmetrically increased left ventricular wall thickness (in the absence of hypertension or aortic valvular disease), (ii) hypokinesia and decreased systolic thickening of the interventricular septum and left ventricular posterior wall, and (iii) small to normal size of the left ventricular cavity.

Conclusion

There is evidence for a significant involvement of the heart in AS and other SpA, especially in Reiter's disease. In general, clinical symptoms are related to the severity of the organ affection. Especially, the aortic valve, the aorta and subaortal structures are involved in AS patients. Furthermore, the myocardium and the conduction system, especially the AV node, are more affected than in the general population. HLA B27-associated AV blocks occur without rheumatic disease manifestations. An HLA B27-associated cardiac syndrome consisting of aortic insufficiency and atrial ventricular block has been described. Early features of aortitis including valvular and subvalvular manifestations can be detected by echocardiography already in patients without cardiopulmonary symptoms.

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