

## SCIENTIFIC PAPERS

## Heart conduction disturbance: an HLA-B27 associated disease

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## Abstract

In recent studies from Sweden an increased prevalence of HLA-B27 associated diseases and of HLA-B27 was found in an unselected group of men with permanently implanted pacemakers and with a heart block. Furthermore, a significantly increased prevalence of HLA-B27 was found in men with a pacemaker who had no clinical or radiological signs of HLA-B27 associated disease. To obtain more insight into the association between HLA-B27 and heart block, and the possible role of HLA-B27 in causing this block, a study was made of 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 men had ankylosing spondylitis and two patients had an asymptomatic sacroiliitis, but all three were HLA-B27 negative. HLA-B27 was present in five (14%) patients, which is a significantly higher prevalence than in healthy controls (17/292, 6%). This percentage is equal to the percentage of HLA-B27 positivity found in the Swedish study on unselected men with an implanted pacemaker, in whom the presence of an HLA-B27 associated disease had been excluded. It suggests that factors other than HLA-B27 are important in the pathogenesis of heart block in most patients.

Extra-articular features, such as acute anterior uveitis, cardiovascular disease, lung fibrosis, and possibly IgA nephropathy, are listed as disease manifestations of ankylosing spondylitis.<sup>1</sup> Cardiovascular disease is reported in more than 50% of patients with ankylosing spondylitis. Occasionally, sinus node malfunction and

atrial arrhythmias are reported.<sup>2</sup> Aortic regurgitation is found in 2-10% of such patients<sup>3-6</sup> and conduction disturbances in 5-23%; this percentage increases up to 33% after more than 25 years' duration of disease.<sup>3-5-8</sup> Recently, Brewerton *et al* found evidence for cardiomyopathy in more than 50% of patients with ankylosing spondylitis.<sup>9</sup> At histological examination a mononuclear infiltrate, fibrosis, and hyaline sclerosis are found near the aortic valves and aortic root, the atrioventricular node, and adjacent part of the membranous and muscular septum where the proximal part of the conduction system is located.<sup>5-10</sup> In ankylosing spondylitis a high prevalence of the genetic marker HLA-B27 is found. Although in recent years much more has become known about the function of HLA molecules in the immune response, the role of HLA-B27 in the pathogenesis of ankylosing spondylitis remains elusive.<sup>11</sup> An increased prevalence of HLA-B27 is also found in patients with diseases that are often associated with ankylosing spondylitis, but without further signs of ankylosing spondylitis, such as sacroiliitis, seronegative arthritis, and acute anterior uveitis.<sup>1</sup> The prevalence of HLA-B27 and associated diseases was studied in patients with aortic regurgitation. Although several authors found an increased prevalence of ankylosing spondylitis and other spondylarthropathies, HLA-B27 was not increased in the patients without spondylarthropathies.<sup>12-15</sup> In a Swedish group of 223 men who had permanently implanted pacemakers 15 (7%) fulfilled the diagnostic criteria for ankylosing spondylitis,<sup>16</sup> while HLA-B27 was present in 11 of 13 (85%) of these patients tested for HLA-B27.<sup>17</sup> In a later study of this Swedish group HLA-B27 was found in 14 of 83 (17%) permanently paced men with complete heart block

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Accepted for publication  
22 June 1990

## Summary of reports on patients with pacemakers implanted and the presence of HLA-B27 and associated diseases

Author (reference)	Number of patients	Ankylosing spondylitis No (%)	Spondylarthropathy No (%)	Sacroiliitis No (%)	HLA-B27 No (%)	HLA-B27 in controls (%)	Remarks
Bergfeldt <sup>16</sup> 17	223 men	15 (7)	28 (13)	19 (9)	36/109 (33)*		Men with pacemaker
Bergfeldt <sup>16</sup> 17	142 men	11 (8)	20 (14)	14 (10)	30/101 (30)†		Men with pacemaker and complete heart block
Bergfeldt <sup>18</sup>	83 men	Excl.‡	Excl.	Excl.	14 (17)	6	Men with pacemaker and complete heart block, without HLA-B27 associated disease
Bergfeldt <sup>19</sup>	85 women	0	0	0	7 (8)	6	Women with pacemaker and heart block
Present study	35 men	1§ (3)	1§ (3)	3§ (9)	5 (14)	6	Men with pacemaker and heart block, known causes excluded

\*HLA-B27 not determined in 114 patients.

†HLA-B27 not determined in 41 patients.

‡Excl: patients with these phenomena were excluded from the study.

§HLA-B27 negative.

in whom the presence of radiological or clinical signs of an HLA-B27 associated disease had been excluded.<sup>18</sup> In contrast, there was no increase of HLA-B27 in the women with pacemakers installed<sup>19</sup> (table).

These findings are reported from Scandinavia where the prevalence of HLA-B27 in the general population is relatively high.<sup>1</sup> Bergfeldt *et al*, however, found a prevalence of HLA-B27 in the controls of 6%.<sup>18 19</sup> It was thought worthwhile confirming the Swedish results in a country with a lower prevalence of HLA-B27 in the general population. This study was therefore undertaken to investigate the presence of HLA-B27 and its associated diseases in a Dutch population of male patients with pacemakers and with conduction disturbances of unexplained origin.

#### Patients and methods

From a group of 350 men fitted with a permanent pacemaker who attended our department of cardiology a group of 35 was selected who had a conduction disturbance without evident cause. Patients with known myocardial infarction or cardiac surgery before the pacemaker implantation and with congenital heart disease or acquired heart valve disease were excluded from the study. Informed consent was obtained from each patient, and then a clinical history was taken and a physical examination performed. Attention was paid to signs and symptoms associated with the presence of ankylosing spondylitis and with other HLA-B27 related disorders. A plain pelvic radiograph was obtained and scored for the presence of sacroiliitis by two independent observers. Blood samples were taken and HLA typed according to standard procedures.<sup>20</sup>

Five hundred controls (292 male) were chosen randomly from a group of about 18 000 blood donors attending the Leiden bloodbank. A Woolf-Haldane analysis was performed to examine a possible difference in the prevalence of HLA-B27 in those with a pacemaker and in the controls.<sup>21</sup>

#### Results

A pacemaker had been implanted in 35 men with a conduction disturbance without evident cause. Eighteen had a complete atrioventricular block and 17 had a second or first degree block or a bundle branch block, four with additional sick sinus syndrome. The indications for pacemaker implantation had been collapse, loss of consciousness, dizziness, or objective decrease in exercise tolerance in combination with these diagnoses.

Fourteen of these 35 men had a history of back pain, which was inflammatory in eight. Three patients had limitation of movement of the lumbar spine, one of whom had back pain which was inflammatory. One patient had bilateral sacroiliitis grade 4-4 and had earlier been diagnosed as having ankylosing spondylitis. Two patients without back pain had unilateral sacroiliitis; all other radiographs were normal.

Five of the 35 (14%) patients were positive for

HLA-B27, which is significantly different from the 17 of the 292 (6%) male donors ( $p < 0.05$ ). None of the five HLA-B27 positive patients showed signs of ankylosing spondylitis, spondylarthropathy, or sacroiliitis. The patient with ankylosing spondylitis and both patients with sacroiliitis were negative for HLA-B27. The conduction defects in these five patients included the following: a complete atrioventricular block in one, second degree atrioventricular block in one, and a combination of several conduction defects in the other three patients. Two of the last three patients also had a sick sinus syndrome.

#### Discussion

This study indicates that the prevalence of HLA-B27 in men with permanent pacemaker implantation because of conduction disturbance of unknown origin is significantly higher than the prevalence of HLA-B27 in healthy male blood donors. The results of our study confirm and are complementary to the findings of Bergfeldt *et al* (table). In his initial studies of unselected men with pacemakers a high percentage of ankylosing spondylitis, other forms of spondylarthropathies, and HLA-B27 associated disease (and therefore HLA-B27) were found.<sup>16 17</sup> In a later study Bergfeldt *et al* concentrated on a group of men with permanent pacemaker implantation in whom clinical or radiological signs of HLA-B27 associated disease had been excluded.<sup>18</sup> The prevalence of HLA-B27 (17%) in this group was still statistically higher than the prevalence of HLA-B27 in a control group (6%), and corresponds with the prevalence in our patient group. The percentage HLA-B27 in the controls is lower than expected in a Scandinavian population.<sup>1</sup>

The number of patients in our study was small, but these patients were selected from a considerable number (350) of men with pacemakers followed up at a large university hospital. In our group we found only one patient with a spondylarthropathy, which is no higher than expected in a group of 35 randomly selected subjects. When our studies and those of Bergfeldt *et al* are combined it becomes apparent that the prevalence of HLA-B27 is doubled in men treated with pacemakers who have conduction disturbance but are without other signs or symptoms of an HLA-B27 associated disease. From these findings it can be argued that the presence of HLA-B27 in men is associated with conduction disturbances. Despite increasing understanding of the HLA system and immunopathology in patients with ankylosing spondylitis, the exogeneous factor that causes the disease remains unknown. Therefore, speculation about such a factor in patients with heart block may be premature. It is remarkable that in patients with a heart block of unknown origin the prevalence of HLA-B27 is significantly increased compared with controls and is about the same as the prevalence in a unselected group of patients with heart block. So, in contrast with its tentative role as a cause of ankylosing spondylitis, HLA-B27 may be of less importance than other as yet unknown factors in causing a

heart block. Further research should be done to gain further insight into the role of HLA-B27, other genetic markers, and exogenous factors in conduction disturbances.

We are indebted to Mrs G M Th Schreuder and colleagues for HLA typing.

- 1 Calin A. Ankylosing spondylitis. In Kelly W N, Harris E D, Ruddy S, Sledge C B, eds. *Textbook of rheumatology*. Philadelphia: Saunders, 1989: 1021-37.
- 2 Thomson N H, Hørslev-Petersen K, Beyer J M. Ambulatory 24-hour continuous electrocardiographic monitoring in 54 patients with ankylosing spondylitis. *Eur Heart J* 1986; 7: 240-6.
- 3 Graham D C, Smythe H A. The carditis and aortitis of ankylosing spondylitis. *Bull Rheum Dis* 1958; 9: 171-4.
- 4 Kinsella T D, Johnson I G, Sutherland R I. Cardiovascular manifestations of ankylosing spondylitis. *Can Med Assoc J* 1974; 21: 1309-11.
- 5 Bulkley B H, Roberts W C. Ankylosing spondylitis and aortic regurgitation. Description of the characteristic cardiovascular lesion from study of eight necropsy patients. *Circulation* 1973; 48: 1014-27.
- 6 Sukenik S, Pras A, Buskila D, Katz A, Snir Y, Horowitz J. Cardiovascular manifestations of ankylosing spondylitis. *Clin Rheumatol* 1987; 6: 588-92.
- 7 Bernstein L, Broch O J. Cardiac complications in spondylarthritis ankylopoietica. *Acta Med Scand* 1949; 135: 185-94.
- 8 Bergfeldt L, Edhag O, Vallin H. Cardiac conduction disturbances, an underestimated manifestation in ankylosing spondylitis. *Acta Med Scand* 1982; 212: 217-23.
- 9 Brewerton D A, Goddard D H, Moore R B, et al. The myocardium in ankylosing spondylitis. A clinical, echocardiographic and histopathological study. *Lancet* 1987; i: 995-8.
- 10 Bergfeldt L, Edhag O, Rajs J. HLA-B27-associated heart disease. Clinicopathologic study of three cases. *Am J Med* 1984; 77: 961-7.
- 11 Feltkamp T E W. New views on B27 associated diseases. *Neth J Med* 1989; 35: 119-22.
- 12 Calin A, Fries J F, Stinson E B, Payne R. Normal frequency of HL-A B27 in aortic insufficiency. *N Engl J Med* 1976; 294: 397.
- 13 Hollingworth P, Hall P J, Knight S C, Newman R. Lone aortic regurgitation, sacroiliitis, and HLA B27. Case history and frequency of association. *Br Heart J* 1979; 42: 229-30.
- 14 Tan P L J, Butler M J, Woodfield D G, Jacobson C, Grigor R R, Caughey D E. HLA antigens in isolated aortic incompetence. *J Rheumatol* 1980; 7: 757-9.
- 15 Qaiyumi S, Hassan Z U, Toone E. Seronegative spondylarthropathies in lone aortic insufficiency. *Arch Intern Med* 1985; 145: 822-4.
- 16 Bergfeldt L, Edhag O, Vedin L, Vallin H. Ankylosing spondylitis: an important cause of severe disturbances of the cardiac conduction system. *Am J Med* 1982; 73: 187-91.
- 17 Bergfeldt L. HLA B27-associated rheumatic diseases with severe cardiac bradyarrhythmias. Clinical Features and prevalence in 223 men with permanent pacemakers. *Am J Med* 1983; 75: 210-5.
- 18 Bergfeldt L, Möller E. Complete heart block—another HLA B27 associated disease manifestation. *Tissue Antigens* 1983; 21: 385-90.
- 19 Bergfeldt L, Möller E. Pacemaker treated women with heart block have no increase in the frequency of HLA-B27 and associated rheumatic disorders in contrast to men—a sex linked difference in disease susceptibility. *J Rheumatol* 1986; 13: 941-3.
- 20 Van Rood J J. Microlymphocytotoxicity method. In: Ray J C, ed. *Manual of tissue typing techniques*. Bethesda: National Institutes of Health, 1979: 104-5.
- 21 Svevgaard A, Jersild C, Staub Nielson L, Bodmer W F. HLA antigens and disease: statistical and genetical considerations. *Tissue Antigens* 1974; 4: 95-105.