Prevalence and clinical characteristics of ankylosing spondylitis in Iceland – a nationwide study

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Abstract

Objective

To determine the prevalence and clinical characteristics of ankylosing spondylitis (AS) in the Icelandic population, which carries a high prevalence of HLA-B27.

Methods

A nationwide search was performed by screening hospital records and private rheumatology services for cases of AS in association with an on-going genetic study. Individuals diagnosed with AS according to the modified New York criteria were asked to participate in the study by answering a standardised questionnaire and to undergo an interview and clinical evaluation.

Results

A total of 256 individuals fulfilled the modified New York classification criteria for AS (169 male, 87 female); 84% of these individuals were HLA-B27 positive vs. 15% in the population ($p<10^{-16}$). Of those contacted 223 patients (87.1%) answered the standardised questionnaire and were included in the study. The prevalence of AS in Iceland was 0.13% (CI 0.11–0.14%). A highly conservative prevalence number, based only on clinically evaluated patients, gave prevalence of 0.10% (CI 0.09–0.11%). Mean age at onset of symptoms was 24±8 years and at diagnosis 32.1±10.2 for male and 34.2±10.1 for female patients (not significant). Female patients more often had arthritis in peripheral joints and male patients were more often diagnosed with iritis. Prostatitis was experienced by 27% of male patients.

Conclusion

AS is less common in the Icelandic population than reported in various Caucasian populations with a similar prevalence of HLA-B27.

Key words

Ankylosing spondylitis, prevalence, demographics, nationwide

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The study was funded by the research foundations of the University Hospital in Iceland, the Society for Rheumatology in Iceland and the Wyeth Rheumatology Foundation in Iceland.

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Received on October 1, 2009; accepted in revised form on December 10, 2009.

Competing interests: none declared.

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease, characterised by low back and buttock pain with morning stiffness of insidious onset, usually beginning in adolescence or early adulthood (1-3). Sacroiliitis with syndesmophyte formation can in advanced disease lead to spinal ankylosis or formation of so-called bamboo spine (4). Arthritis of peripheral joints, costochondritis and enthesopathy are also commonly described (1-4). Extra-articular manifestations of AS include iritis (25–40%) (5), prostatitis (13–83%) (6, 7) and asymptomatic gastrointestinal tract involvement (69%) has also frequently been described (8). Cardiac and pulmonary involvement seems to be less common (9, 10). The diagnostic criteria most often used are the modified New York criteria published in 1984 (11, 12). These criteria involve both clinical and radiological aspects.

AS has a strong association with HLA-B27 and the prevalence of AS in different cohorts frequently relates to the prevalence of this MHC molecule in the study population (13). The majority or up to 95% of Caucasians with AS carry the HLA-B27 antigen compared to around 8–14% in the background population (14, 15). Population-based studies have previously reported considerable variability in the prevalence of AS, ranging from 0.1–1.4% (2, 16-19) and up to 6% in Canadian Haida Indians (20). A study from Tromsö, Norway, which represents a population with a high frequency of HLA-B27, reported a prevalence of 0.31% for AS, including both primary and secondary forms (21). However, to our knowledge no nationwide study on the prevalence and clinical presentation of AS has up to now been published.

Our goal in this study was to determine the prevalence of AS on a nationwide basis in Iceland and to describe the demographics and clinical features of AS in the Icelandic population, which is characterised by a high prevalence (15%) of the HLA-B27 molecule.

Materials and methods

Study group

The study involved all known patients with AS in Iceland. Patients were recruited from three main sources, first, from a database of 1557 patients participating in ongoing genetic studies of AS and inflammatory bowel diseases (22). This database included not only clinical data on the index cases but also of all available relatives and other family members of these patients, regardless of whether they were reported to have AS or not. From this database, 205 individuals who were alive in 2005 and who had been diagnosed as having AS with the diagnosis verified by a rheumatologist (AJG) were included in the present study.

The second source was an electronic registry of patients admitted to the two major hospitals in Iceland, who both have rheumatologic specialist services: the Landspitali-University Hospital in Reykjavík (LSH) and the University Hospital in Akureyri (FSA). The LSH serves as a primary hospital for Reykjavik and its suburbs and it is the only secondary and tertiary care hospital in Iceland. The FSA serves as a primary hospital for the northern and eastern part of Iceland. A systematic search of AS and sacroiliitis according to the International Classification of Diseases (ICD) 10th diagnostic registry, including the following codes: M 45, M 45.5, M45.9, M 46 and M 46.9, was performed in all hospital records. This source yielded an additional 54 patients who had been diagnosed with AS and who were alive in 2005.

The third source was a personal call to all private rheumatology services (six rheumatologists were working partly and four solely with private praxis; thus ten rheumatologists are running a private clinic in Iceland at the time of the study) in Iceland to report patients to the study. This yielded 64 additional patients who had been diagnosed with AS and who were alive in 2005.

In Iceland every resident is issued a specific security number which allows a combination of individualised information from different sources without mixing data between individuals. The three sources named above yielded 323 patients, but, since many patients were found in more than one database, the total number of patients with AS in Iceland came to 280 individuals.

Clinical examination

All of these 280 known cases of AS in Iceland were initially contacted by a letter of invitation, followed by a telephone call by our study nurse; 24 individuals (8.6%) could not be reached or did not respond. Of the remaining cases 256 or 91.4% of the original study group agreed to participate in the study. All participants were interviewed and examined by the same rheumatologist (AJG). All participants also were asked to answer an extended questionnaire in connection with the genetic study and 223 patients (87.1%) filled out and returned the questionnaire.

Inclusion criteria

The inclusion criteria used for this study were the modified New York criteria for classification of spondylitis ankylopoetica or AS (12), requiring that patients had to have a radiological criterion of sacroiliitis grade >2 bilaterally or grade 3 or 4 unilaterally and at least one of the three following clinical signs: 1) Low back pain and stiffness for more than three months that improve with exercise but are not relieved by rest; 2) Limitation of motion of the lumbar spine in both the sagittal and the frontal plane; 3) Limitation of chest expansion relative to normal values correlated for age and sex.

Patients who did not have active arthritis or inflammatory back pain at evaluation were included if they had been diagnosed with AS by a rheumatologist and were taking remitting drugs at the time of the study. Meanwhile, patients who reported a diagnosis of a rheumatic disease other than AS when interviewed, or who were observed to have another rheumatic condition when examined, were excluded from the study. Furthermore, patients with AS associated with psoriasis were also excluded from the present study as the group of patients with psoriatic arthritis in Iceland has recently been reported separately (23). Of the 256 patients examined, 33 (12.9%) were excluded from the prevalence analysis.

Disease assessment

Chest expansion was measured on maximal inspiration after forced maximal expiration, at the level of the fourth intercostal space in males and just below the breasts in females. The normal values were set at ≥6 cm for males and ≥4.5 cm for females, as normal values of chest expansion are sex dependent. Cervical flexion, extension and rotation were evaluated according to standard clinical measurements and lumbar flexion ability was evaluated by the Schober index and measured in centimetres (cm) (24). Extent of extraspinal symptoms, *i.e.* peripheral joint involvement, was also assessed according to standard clinical evaluation.

Concerning systemic manifestastions of, for example, iritis and prostatitis, the diagnosis was reviewed by one of the study members (AJG) with the requirement that these manifestations were confirmed by physicians at the time of occurrence, *e.g.* ophthalmologist or rheumatologist in the case of eye inflammation and urologist, general physician or rheumatologist in the case of prostatitis, respectively.

All radiographs, computed tomographs and magnetic resonance imaging were re-evaluated by members of the study group.

Whole blood was drawn for later genetic studies and for extended typing of the major histocompatibility complex molecules to estimate the prevalence of HLA-B27 (Dynal HLA-Kit, F. Hoffmann-La Roche Ltd, Basel, Switzerland). A total of 524 randomly chosen healthy volunteers were used as controls and tested for the HLA-B27 antigen, and of those 15.41% turned out to be positive for HLA-B27 (25).

Data analysis

The study data were stripped of information allowing identification of individuals before the analysis of data began and the code for this information was kept in a separate, encrypted database. Point prevalence was based on all living individuals in Iceland on the 31st of December in 2005 and on those who were known to have AS according to the study protocol. The crude annual incidence rate was also calculated based on the year of diagnosis of AS and expressed per 100,000 of the total midyear population for each year (26).

Informed consent was obtained from all the participants in the study. The study was approved by the National Bioethics Committee of Iceland (approval no. 98-059) and by the Icelandic Data Protection Authority (2001/36).

Data were analysed using R-statistical software. Fisher exact tests were used for comparisons. We calculated 95% confidence intervals for prevalence rates using binomial distributions. All reported *p*-values were based on 2-tailed analyses.

Results

Prevalence

According to Statistics Iceland there were 220,441 individuals living in Iceland aged 18 years and older at the end of December 2005 (26). This means that the point prevalence of AS in Iceland when calculated from the 280 individuals with hospital or outpatient clinic diagnoses of AS was 127 per 100,000 (95% CI 112–142). Of the 256 individuals who were invited to participate in the study for clinical evaluation, AS was confirmed according to the inclusion criteria in 223 or 87.1%. Assuming that no case of AS would have been confirmed among the 34 individuals who did not come for re-evaluation of their disease, a highly conservative prevalence estimate of 101 per 100,000 (95% CI 88–114) can be calculated. Conversely, if all these individuals had AS the prevalence estimate would be 112 per 100,000 (95% CI 98–126). However, as these patients had all been previously diagnosed with AS, and there was no obvious selection bias regarding the individuals who could not be reached for clinical re-evaluation, we extrapolated the inclusion ratio for the patients who were examined clinically to all the 280 patients in the original study group, correcting for age and sex, resulting in an adjusted prevalence ratio of 104 per 100,000 (95% CI 91–117).

The prevalence of AS was significantly higher in males than in females; 132 per 100,000 male inhabitants (95% CI 110-153) *vs.* 71 per 100,000 female inhabitants (95% CI 56-88), $p>0.0001$. Thus, the male *vs.* female ratio was 1.85.

Demographics

Demographic data on the 223 patients who satisfied the inclusion criteria and delivered completed questionnaires on their past medical history, use of medication and clinical symptoms of their AS disease are presented in Tables I and II. The male patients had a similar age of onset of symptoms related to their AS, but were diagnosed around two years younger than the female patients (32 vs. 34 years); thus they had about a year shorter diagnostic delay, but these differences were not significant (Table I).

Table I. Demographic data for 223 patients with AS.

Demographic data	Male n=145	Female n=78	*p*-value
Age at onset of symptoms; mean±SD years	23.6 ± 8.4	24.1 ± 8.9	0.55
Age at diagnosis of AS, mean±SD years	32.1 ± 10.2	34.2 ± 10.1	0.13
Diagnostic delay, mean±SD years	8.3 ± 7.7	9.6 ± 10.0	0.87
Clinical characteristics			
Limited chest expansion; n (%)	65 (44.8%)	22 (28.2%)	0.021
Modified Schober; mean±SD cm	3.50 ± 1.63	3.84 ± 1.26	0.09
Limited flexion/extension of neck; n (%)	56 (38.6%)	30 (38.5%)	1
Limited rotation of neck; n (%)	67 (46.2%)	35 (44.9%)	0.89
Active peripheral arthritis; n (%)	18 (12.4%)	15 (19.2%)	0.23
HLA-B27 positive; no (%)	124 (85.5%)	63 (80.8%)	0.34

Table II. Self-reported pain and history of joint inflammation in 145 male and 78 female AS patients.

Symptoms of AS	Male n=145 (%)	Female n=78 (%)	*p*-value
Pain problem	**133 (91.7)**	**74 (97.4)**	**0.15**
Lumbar spine	84.9%	77.0%	0.69
Buttock	53.4%	52.7%	1.00
Thoracic spine	31.6%	27.1%	0.44
Sternum	25.6%	22.9%	0.74
Joint inflammation	**64 (44.1)**	**52 (66.7)**	**0.0013**
Hip	53.1%	48.1%	0.485
Knee	25.0%	30.8%	0.429
Shoulder	20.3%	25.0%	0.737
Eye inflammation - iritis	**55 (37.9)**	**24 (30.8)**	**0.31**
Prostatitis	**39 (26.9%)**	**–**	**–**

Onset of AS and annual incidence

The mean age at onset of symptoms related to AS was 24±8 years, attesting that around 80% of both male and female patients suffered onset of symptoms before thirty years of age; the peak incidence was 16 to 20 years for male patients whereas for female patients it was during their late thirties (Fig. 1). The mean age of diagnosis was 32.1±10.2 for male patients and 34.2±10.1 for female patients.

Of the 223 individuals included in the study, 214 or 96%, reported the year of diagnosis. The crude annual incidence rate for the period 1947 to 2005 ranged from 0.44 to 5.48 per 100,000 inhabitants (Fig. 2).

The majority of patients or 58.7% reported an insidious onset of the disease. Juvenile onset of symptoms (<16 years) was reported by 35 patients (15.7%); 22 (15.2%) male and 13 (16.7%) female patients. Pain was reported as the presenting symptom in 92.8% of both male and female patients; 91.7% vs. 94.9%, respectively. Lower back pain was the most common pain location in both sexes (84.9% *vs*. 77.0 %) and buttock pain was the second most common pain location (male 53.4%; female 52.7%). Table II shows location of self-reported pain and inflammation in both males and females.

Limited flexion and extension, and rotation of the head were the same in both sexes (Table I). Lumbar flexion measure by modified Schober index was also similar in male and female patients, but a significantly higher number of male patients had limited thoracic expansion (44.8% vs 28.2%; p=0.02) (Table I).

HLA-B27

The prevalence of HLA-B27 positive individuals was 84%, with no significant difference observed between the sexes. Analysis by a multiplicative model showed the prevalence of AS among HLA-B27 positive individuals to be 0.71% (CI 0.64%–0.84%), while we found a prevalence of only 0.028% (CI 0.020%–0.036%) in those without the HLA-B27 molecule, *i.e*. HLA-B27 negative individuals.

Patterns of peripheral joint involvement

A total of 116 patients (52%) had a history of peripheral arthritis; 44.1% of the male patients and 66.7% of the female patients (p=0.0013). The most frequent arthritis conditions were reported by the patients themselves in the hip joints (53% in males and 48% in females) and knee joints (25% in males and 31% in females), followed by arthritis in the ankle and the shoulder joints. Polyarticular involvement was reported by 35 out of 145 male patients (24%) and in 19 out of 78 (24%) female patients. On the day of examination 18 male patients (23%) and 15 female patients (19%) had signs of arthritis in their peripheral joints. Achilles tendonitis was observed in 21% of both males and females, while plantar fasciitis was observed in 6% of the male patients and 12% of the female patients (p=0.19).

Extra-articular involvement

The most commonly reported extra-articular sign associated with AS in both males and females was iritis; 38% *vs*. 30.8% (difference between sexes: p=0.31). In most cases the iritis was unilateral, but 15 out of 55 male (10.3%) patients with a history of iritis and two out of 24 (2.6%) female patients gave a history of bilateral involvement of the eyes (p=0.08). The second most common extra-articular manifestation reported by male patients was prostatitis, which 27% of the male patients reported. Other commonly reported extra-articular manifestations were cardiac arrhythmias in males and females, 14.5%

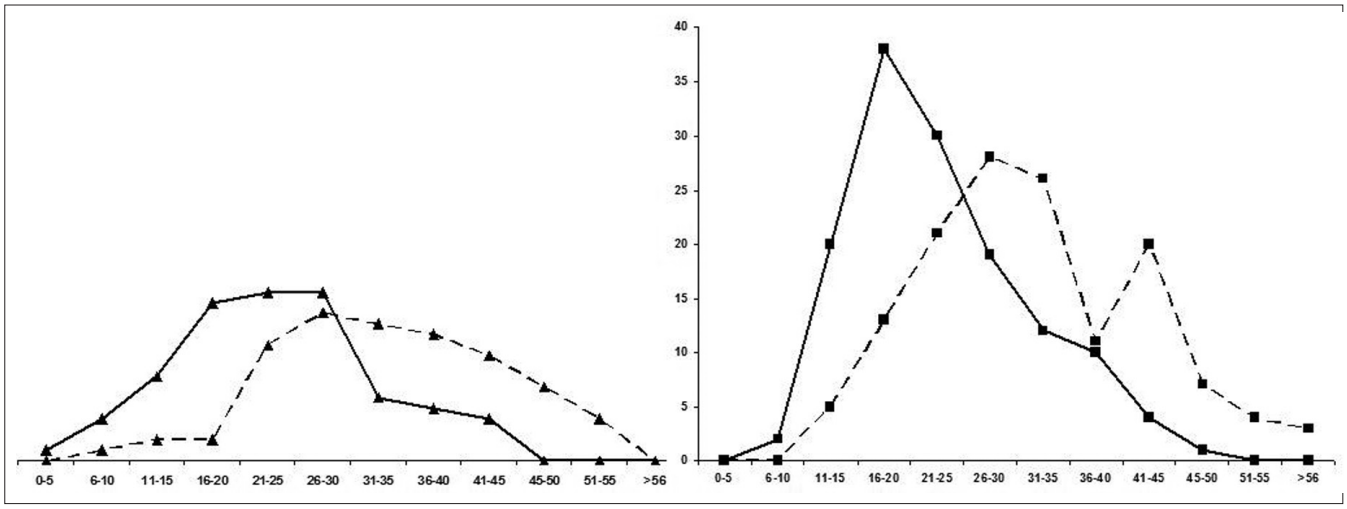

Fig. 1. Onset of symptoms related to ankylosing spondylitis (AS) and age of diagnosis in 145 male (left) and 78 female (right) patients with AS. The full line shows the age of onset of symptoms related to AS, while the broken line shows age at diagnosis of AS.

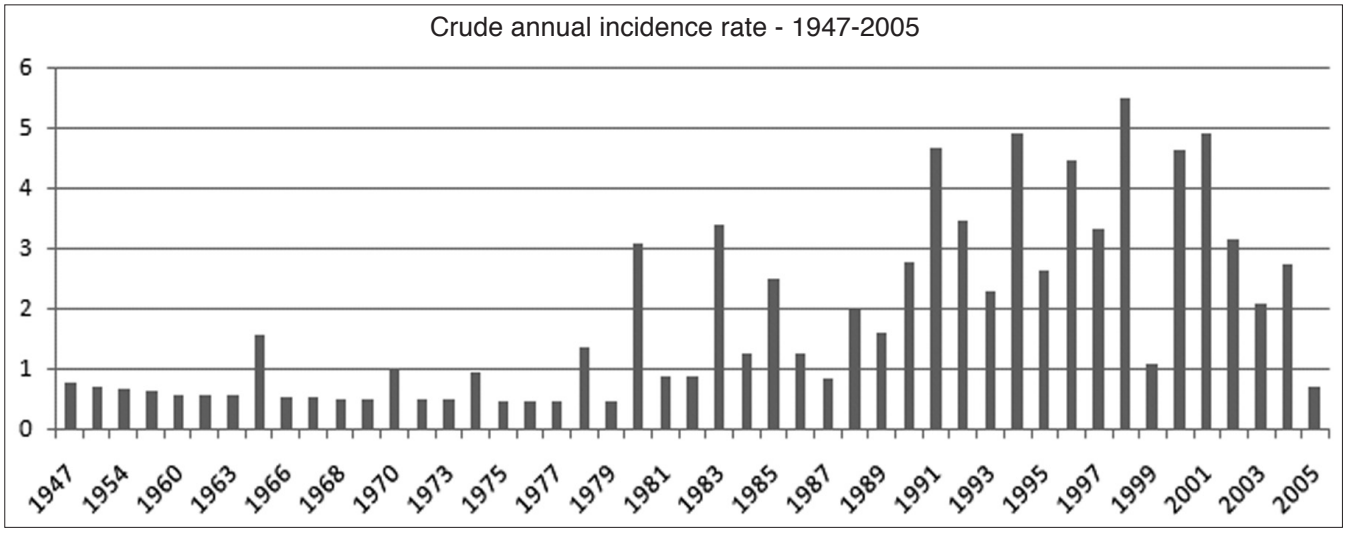

Fig. 2.

and 17.9%, respectively. However, only 1.4% of the male patients reported having a cardiac pacemaker implanted due to atrio-ventricular block, while none of the female patients had a pacemaker. One male patient was found to have aortic valve insufficiency. No information was collected as to whether any patient suffered from pulmonary fibrosis.

Primary vs. secondary AS

Two female patients (2.6%), but no male patients, had been diagnosed with Mb Crohn's after the onset of their AS, while nine of the male and six of the female participants had a history of colitis ulcerosa that had been diagnosed simultaneously or after the onset of their AS, respectively. Patients with psoriatic spondylarthritis were excluded from the present study, as those have been reported separately for the same population of interest (23).

Treatment

Sixty-four percent of male patients were on some specific anti-rheumatic treatment for their AS, compared to 50% of the female patients (p=0.0013). More female patients received regular physiotherapy treatment than male patients; 50% *vs.* 24% (p=0.00015), respectively. Most frequently the patients were treated with infliximab (n=77), sulfasalazine (n=60), or methotrexate (n=25), while 79 patients were using NSAIDs and 10 celecoxib on a regular basis.

Discussion

This cross-sectional study was based on a nationwide cohort of patients with AS in a population with a high prevalence of the MCH molecule HLA-B27. We recruited patients not only through hospital records but also from specialist out-patient clinics and from an extended database focusing on the genetics of AS in Iceland. Thus, our patient group represent a clinically relevant population of AS patients. All patients were re-evaluated by the same experienced rheumatologist and we systematically collected clinical data from 280 cases with AS in an adult population of around 220,000 individuals. Our results demonstrated a disease prevalence of 0.13%, which was in the lower range of previous reported

prevalence of 0.1–1.4% (2, 16-18), independently of whether we compare our result with other Nordic countries (2, 16, 17) or with data from the Mediterranean (18, 19, 27), our prevalence data especially were much lower than reports from areas with a high prevalence of the HLA-B27 molecule, *e.g.* of 0.31% (21).

The crude annual incidence of AS in Iceland was retrospectively found to be 0.44 per 100,000 inhabitants in the last mid-century, which increased up to as high as 5.48 in 1998, but was around 3 per 100,000 the latter decades of the study period. In the early eighties the incidence seemed to increase, probably due to the increased number of practising rheumatologists in Iceland and better access to computed tomography and later to magnetic resonance imaging for diagnostic purposes. The incidence in the later period is lower than what has been reported in Norway (21), Finland (2) and Minnesota, USA (28), but higher than in Greece (19).

One of the possible explanations for these differences in prevalence in the present study and those from northern Norway (21) and Lithuania (29) is that our study extended over the whole of Iceland and might therefore reflect regional differences in recruitment as all participants were invited to our research centre in Reykjavik. However, we did not find any differences in disease prevalence of AS depending on rural or urban areas of Iceland (data not shown). Another explanation of this discordance is that the present study did not include patients with AS associated with psoriatic arthritis, as this has recently been reported for Iceland (23). If we add those patients with AS in our previous study on psoriatic arthritis to the present cohort, the prevalence of AS migth increase up to 0.19%. Thus our prevalence is still lower than reported in high HLA-B27 geographic areas. Other explanations for this discordance might be that the HLA-B27 subclasses in Iceland are different or Icelanders may have some other genetic combination than in the other countries, which may play a role in the pathogenesis of AS. Lastly and even more important, various environmental factors in different populations may have strong influences on the pathogenic processes of AS.

Our observation of a male to female ratio of a little less than 2:1 was clearly lower than previously reported. Earlier studies have reported a male to female ratio of AS up to 10:1 (30), but more recent studies have reported lower male to female ratios or approaching 2-3:1 (31). In this context, we found female dominance in our psoriatic arthritis cohort of a male *vs.* female ratio of 1:2 (23) while most other studies report a male *vs.* female ratio closer to 1:1 for psoriatic arthritis. Thus, this difference may be a true regional difference. However, other factors like excellent access to diagnostic tools, *e.g.* computed tomography and magnetic resonance imaging, may have improved the diagnosis of AS in female patients in Iceland compared to other study areas.

The present study cohort seems to represent a traditional patient group of AS patients in respect to clinical symptoms of insidious onset of low back and buttock pain with morning stiffness, as well as the prevalence of oligoarthritis in large joints in the lower extremities, *i.e.* hip and knee. As expected, female patients had their onset of AS-related symptoms some years later than what male patients reported. However, to our surprise and in contrast to clinical experience and the report by Dincer *et al.* (32) our female patients had just around one year of diagnostic delay compared to our male patients, *i.e.* 9.6 *vs.* 8.3 years. This may reflect active intervention of diagnostic procedures in Iceland, as previously discussed.

Male AS patients more often reported a history of iritis than female patients, *i.e.* 38% of our male patients had a history of iritis, most frequently unilateral, while only 31% of our female patients had a history of iritis. Other differences between male and female patients in our cohort were that female patients seem to have more frequently had arthritis problems in their peripheral joints than did the males. These findings conform to other reports (33). However, a much higher percent reported a history of involvement of peripheral joints. This may reflect differences in collecting data. In the case of prostatitis, an earlier study reported prostatitis as a frequent systemic manifestation of AS (6, 7). Lately not much particular attention has been paid to this problem. The present study suggests that prostatitis might be a bigger issue in AS than rheumatologists are currently aware of. Unfortunately we did not register active symptoms of urethritis or balanitis at the time of inclusion to the study. Many AS patients of both sexes reported a history of unspecific cardiac arrhythmias and two male patients had an implanted cardiac pacemaker due to an atrioventricular block (AV-block), and another 60 year old male patient had a history of aortic valve insufficiency. A genetically HLA-B27 linked cardiac syndrome has been defined, *i.e.* the combination of conduction system abnormalities and aortic regurgitation (9), and AS is also reported to be associated with a greater risk than expected of cardiac lesions (34). Meanwhile, no patient reported a lung disorder, *i.e.* pulmonary fibrosis; thus, this pulmonary complication of AS seems to be very infrequent or under-diagnosed in our patient cohort. Our study was not designed to investigate the mortality rate of our AS patient population, which has been reported to be greater than for the normal population (34).

The prevalence of HLA-B27 in various populations seems to correlate to some extent with the population prevalence of AS in the same cohort, suggesting that HLA-B27 mediates important antigen presentation which has a role in the pathogenesis of AS (5, 35), More than 90% of Caucasians in Western Europe with AS are HLA-B27 positive, compared to around 8% (5) in the general background population, although the prevalence of HLA-B27 varies in different populations, which may reflect the importance of other pathogenetic factors, including various environmental factors. HLA-B27 positive patients seems to experience disease symptoms at a younger age and they also more frequently have iritis and arthritis in peripheral joints, though homozygosity for HLA-B27 does not effect the clinical presentation of AS (36). Interestingly, in our study population the prevalence of AS in HLA-B27 positive individuals

was 0.71%, while only 0.03% in those who were HLA-B27 negative.

The main strength of our study is that all available patients from both community and hospital based data sources with a verified diagnosis of AS were recruited. Each source has different selection biases that complement the other, as only 43 cases of 280 were harvested from the same source. All these individuals were re-evaluated according to a predefined routine by an experienced rheumatologist. This is important, as most previous studies of the prevalence and demographics of AS have relied either on patient records (2, 19, 21) or self-report by questionnaires (37). In contrast, the main shortcoming of our study is that the participants were not recruited randomly from the population living in Iceland, but such a strategy is hardly realistic for complex diseases with a prevalence as high as for AS. It is likely that relatively mild cases of AS are not diagnosed according to international classification criteria, especially in patients who only attend health centres. However, the majority of patients with inflammatory joint diseases in Iceland attend out-patient specialist clinics. Thus, our adjusted AS prevalence of 0.1% is still probably an underestimate. Further studies are clearly needed to refine epidemiological information on AS, including sex ratios, as well as prospective studies with multiple follow-up visits to monitor the disease course over long periods.

In conclusion, AS seems to be less common in the Icelandic population than reported in other Scandinavian countries and Minnesota, USA, despite the higher population prevalence of HLA-B27 in Iceland. However, the prevalence is similar to that in northern Norway, where the prevalence of HLA-B27 is also high.

Acknowledgments

We would like to thank Valdimar B. Hauksson and Bjarni V. Halldórsson at the statistics department at deCODE Genetics.

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