Mortality in ankylosing spondylitis

J. Zochling[1], J. Braun[2]

[1]Research Institute, Hobart, Australia;
[2]Rheumazentrum-Ruhrgebiet,
St. Josefs-Krankenhaus, Herne, Germany.

Jane Zochling, MBBS, MMed (ClinEpi), PhD, Research Fellow and Rheumatologist; Jürgen Braun, MD, Professor of Medicine and Rheumatology.

Please address correspondence and reprint requests to:
Jürgen Braun, MD,
Professor of Medicine and Rheumatology,
Rheumazentrum-Ruhrgebiet,
St.Josefs-Krankenhaus, Landgrafenstr. 15,
44652 Herne, Germany.
E-mail:
J.Braun@rheumazentrum-ruhrgebiet.de

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Abstract

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease which causes pain along with loss of physical function and quality of life over many years. It has also been shown to increase mortality compared to the general population, independent of treatment modalities. Cardiovascular deaths are increased, and recent studies suggest both an abnormality of lipid regulation and microvascular changes. Increased rates of suicide, accidental death, and alcohol-related deaths have also been reported. This review examines rates and causes of increased mortality in AS and highlights a need to focus on cardiovascular risk factors and psychological health in addition to physical disability in patients with AS.

Introduction

Ankylosing spondylitis (AS) is a chronic, inflammatory rheumatic disease which is known primarily for causing a lifetime of pain, impaired physical function, work disability, and decreased quality of life, rather than for shortening life itself. Musculoskeletal manifestations of AS include both inflammation and structural damage, seen as syndesmophytes, erosions, vertebral fractures and ankylosis of the spine, sacroiliac joints and (less commonly) the peripheral joints. Characteristic extra-articular manifestations include aortitis, cardiac conduction defects, pulmonary fibrosis, secondary amyloidosis and inflammatory bowel disease indicating that AS is a systemic disease. Patients with AS also experience premature mortality (1) . This review summarizes published data concerning mortality in AS patients and examines some potentially modifiable risk factors that warrant clinical attention.

The issue of mortality in AS patients first attracted attention in the 1950s. At that time, patients with AS were treated with radiotherapy for spinal pain and stiffness (2), leading to increased mortality rates from haematological malignancy compared to the general population (3, 4). In fact, the initial study was designed to investigate leukaemia as a result of radiotherapy, and not specifically to describe mortality in AS patients. Data on 14.554 patients who had undergone spinal irradiation between 1935 and 1954 were collected from the 87 radiotherapy centres operating in the UK. In addition to confirming a higher mortality from leukaemia and aplastic anaemia in irradiated patients, the study showed that overall all-cause mortality was increased about 1.8-fold in AS compared to the corresponding national death rate, and that this increase could not be ascribed solely to irradiation (4). Higher-than-expected death rates were seen due to non-malignant causes and due to AS itself.

In order to study more directly the underlying mortality in radiotherapy-naïve AS patients, the authors then collected data on 836 patients diagnosed with AS between 1935 and 1957 from clinic records across the UK (5). There were 146 deaths over the follow-up period to January 1968, giving a relative risk of 1.8, higher than expected in the general population. The distribution of causes of death (excluding malignancy) was similar to that reported in the radiotherapy group, with high proportions of deaths attributed to AS and related conditions. There were also increased rates of gastrointestinal, cerebrovascular, circulatory and violence-related deaths. Cancer mortality was not increased (6), and more recently large population-based studies have confirmed that AS does not confer an increased risk of malignant lymphoma (7) or other cancers (8).

Standardized mortality rates (SMR) for AS patients compared to the general population are shown in Table I. The extensive research by Court Brown and colleagues remains the largest study of mortality in AS (4, 5), and subsequent

Table I. Standardized mortality ratios (SMR) in published population studies in AS.

Study (ref)	Year	Location	Past x-ray therapy	Number of patients	SMR
Court Brown (4)	1965	UK	Yes	14554	1.80
Radford (5)	1977	UK	No	836	1.60
Kaprove (9)	1980	Canada	No	62	1.33
			Yes	76	2.62
Khan (11)	1981	USA	No	56	1.32
Smith (36)	1982	UK	Yes (once only)	14111	1.66
Darby (28)	1987	UK	Yes (once only)	14106	1.51
Lehtinen (10)	1993	Finland	No	398	1.50

smaller hospital or clinic-based studies have revealed similarly elevated mortality rates. It is not possible to compare the mortality rates between studies statistically, due to the large variability between study populations, which differ with regard to methods for case recruitment, age and sex distributions, disease duration and treatments the patients have received. Nevertheless, all studies showed a statistically significant elevation in mortality in AS patients compared to the normal population. The use of x-ray therapy for AS in the early- to mid-1900s led to its own increase in mortality, and as such the data have been presented separately depending on past treatment.

Kaprove and colleagues (9) followed 151 Canadian veterans with AS from their enrolment in a prospective study between 1947 and 1949 until June 1976, a minimum of 27 years of follow up, and directly compared the mortality rates between x-ray treated and x-ray naïve patients. Mortality in the x-ray treated group was found to be double that of the untreated group. It was not clear if the two groups were significantly different in severity or duration; the treated patients were slightly younger than the treatment-naïve patients. However, it may be that those who received x-ray treatment had significantly more active or more disabling AS, which contributed to the increase in mortality.

Only one study has directly addressed possible risk factors contributing to the increase in mortality seen in AS patients. Lehtinen (10) studied 398 patients recruited from a hospital-based practice between 1961 and 1969. The mortality rate was 1.5 compared to the normal population, similar to other cohorts. An association was shown between mortality and age, erythrocyte sedimentation rate (ESR), and number of inflamed joints at entry into the study. Patients who died over the 25 years of follow-up were approximately 10 years older at entry than survivors, and therefore lower survival might be expected. Mean ESR was 54.1 mm/hr at baseline in those who died, compared to 38.5 mm/hr in survivors, and mean number of inflamed peripheral joints at baseline in patients who died was higher than in survivors (1.5 compared to 0.7). The association of higher baseline disease activity with subsequent mortality may not necessarily reflect higher disease activity throughout the study, nor a more severe disease course, as it is based on a point measurement early in the disease. Nonetheless, it does suggest that disease activity may play a role in ultimate mortality.

Lehtinen (10) and Khan (11) have shown that mortality rates increase with time from study enrollment at a faster rate than the rise of mortality in the general population. These findings suggest more than just the effect of increasing age on the risk of death. It may be, however, that this difference in rates over time is explained by other factors, such as disease activity or structural damage, and not merely disease duration. Comparative survival rates over 25 years are shown in Table II. Further studies are required to ascertain reliable predictors of increased mortality risk in AS patients.

The attributed causes of death in patients with AS are shown in Table III, although the largest study published to date does not differentiate between the different mechanisms of death caused directly by AS (4). Circulatory death, including ischaemic heart disease, other cardiovascular disease and cerebrovascular disease, is the leading cause of death in all published studies, as in the normal population. Further details concerning different mortality subsets are discussed in turn below.

Musculoskeletal mortality

Although AS was documented as the cause of death in a large number of patients across many of the described studies, the mechanism of death is not always clear, and in many cases deaths were due to extra-articular manifestations of AS. Some of the more obvious musculoskeletal deaths included three spinal fractures (10-12) and one cervical subluxation (9). One patient was described as succumbing to aspiration pneumonia secondary to dysphagia resulting from oesophageal compression by the aorta (12), likely as a result of the abnormal spinal curvature caused by advanced AS.

Cardiovascular disease

Circulatory diseases were the attributed cause of death in the majority of patients with AS in all series (Table III). AS is known to be associated with specific cardiovascular problems in approximately

Table II. Survival rates in AS populations over time.

Study (ref)	Number at baseline	Survival at 5 years	Survival at 10 years	Survival at 15 years	Survival at 20 years	Survival at 25 years
Wilkinson (12)	212	96%	93%	92%	–	–
Khan (11)	56	–	96%	80%	67%	–
Lehtinen (10)	398	92%	84%	76%	67%	62%

Table III. Percentages of acute causes of death in AS patients in different series (n=number of deaths).

Study	No x-ray therapy for AS				Past x-ray therapy		
	Radford n=146	Kaprove n=20	Lehtinen n=152	Khan n=20	Court-Brown n=1582	Kaprove n=34	Wilkinson n=17
Circulatory	37%	40%	42%	45%	27%	50%	18%
Coronary artery disease/ myocardial infarction	–	30%	25%	–	–	29%	12%
Cerebrovascular	12%	0%	11%	18%	6%	9%	6%
Other circulatory	25%	–	6%	27%	21%	–	–
Cancer	14%	15%	13%	9%	17%	21%	29%
Haematologic malignancy	0%	0%	1%	5%	4%	9%	12%
Pulmonary	12%	10%	6%	9%	6%	6%	12%
Renal	3%	0%	3%	0%	3%	6%	0%
Gastrointestinal	6%	0%	6%	5%	6%	0%	0%
Peptic ulcer disease	3%	0%	0%	5%	2%	0%	0%
Infection	3%	–	1%	9%*	8%*	–	18%*
Musculoskeletal	8%	5%	18%	5%	9%	0%	0%
Amyloidosis (secondary)	0%	0%	13%	0%	0.4%	3%	0%
Accidents and Violence	5%	5%	11%	0%	5%	6%	6%

'0%'-no deaths seen for this cause; '-' - the data was not reported.
*all cases reported were tuberculosis.

3-10% of patients, including aortic insufficiency and conduction abnormalities (13). However, there are no published data on the percentage of these cardiovascular problems that lead to death. Although a small number of deaths was attributed to cardiac amyloidosis in one series (14), in general, deaths were usually recorded as 'circulatory' or 'cardiovascular' with little further classification in the published series, based on chart review and linkage to death certificates. Nevertheless an increased circulatory mortality has been consistently shown, independent of previous treatment for AS (Table II).

Similar to rheumatoid arthritis, it has been suggested that AS patients have an increased risk of cardiovascular disease (15), and a recent large population-based study has shown more ischaemic heart disease (prevalence ratio 1.2), peripheral vascular disease (ratio 1.6), atherosclerosis (ratio 1.5), congestive heart failure (1.8) and more cardiovascular risk factors (prevalence ratios between 1.3 and 1.7) in AS patients compared to healthy controls (16). Peters and colleagues (17) have also reported that many of the traditional risk factors for cardiovascular disease are present in the AS versus the general population, including a higher incidence of hypertension, elevated lipids, increased fibrinogen and CRP levels, and poorer physical activity levels. Increased disease activity, as measured by ESR and the Bath AS Disease Activity Index (BASDAI), is associated with a more atherogenic lipid profile. HDLc levels were decreased out of proportion to the decrease in total cholesterol levels in 55 AS patients receiving varying therapies for their spinal disease (18). In addition, treatment of 60 patients with inflammatory rheumatic disease (including 26 with AS) with anti-TNF therapy resulted in an increase in serum HDLc levels (19), supporting the premise that chronic inflammation influences lipid profiles and therefore contributes to cardiovascular risk. Microvascular dysfunction has also been demonstrated in AS patients (20), and shown to improve as patients were treated with anti-tumor necrosis factor biological agents. Van Eijk and colleagues suggest there may be a role of inflammation in impairment of microvascular endothelium-dependent vasodilatation and capillary recruitment, which in turn is related to increased cardiovascular morbidity. Further research concerning the pathogenesis of increased cardiovascular risk in AS patients should be high priority, as many risk factors are likely to be modifiable.

Pulmonary disease

The spectrum of lung disease in AS includes pulmonary fibrosis particularly of the upper lobes, superimposed fungal infections, and atypical infections of the cysts (21); however, an attributable mortality risk has not been described. AS patients have a high prevalence of asymptomatic lung disease (22), although abnormalities are seen on high-resolution CT in up to 40% of patients. These abnormalities are generally non-specific, and it is not clear what factors might contribute to the development of symptomatic lung disease, although poor chest expansion, thoracic spine disease and smoking have all been implicated in patients with radiological lung disease. The investigators suggest that symptomatic lung disease is much less common than radiological lung disease in AS patients, with no clinical pulmonary disease seen in a prospective cohort of 147 consecutive AS presentations (23) by the same authors.

Tuberculosis, probably as a reportable infection, was listed as a cause of death in most of the earlier studies (Table III); however, these data may not be generalizable to modern times with effective therapies available for TB. Overall, lung disease does not appear to contribute greatly to the increased mortality

rates seen in AS patients compared to the general population.

Renal disease

Many forms of renal involvement have been described in AS. The most common renal disease is secondary amyloidosis, seen in 62% of AS patients with renal involvement (24). Amyloidosis appears as a serious complication of AS and other rheumatic diseases in Finland, although its prevalence may be declining (25); nonetheless, once present, the prognosis is poor. The median survival of AS patients after commencing dialysis for amyloidosis is 2.37 years (1.11-4.31), with a 5-year survival of only 30% (14-48%) (25). It has been suggested that hypergammaglobulinaemia may be a poor prognostic sign with regards to renal amyloidosis and uraemia in AS patients, with a disproportionate number of deaths due to renal amyloidosis seen in a small group of patients with hypergammaglobulinaemia compared to those with normal levels as a part of a larger study of mortality in AS (26). After secondary amyloidosis, IgA nephropathy is seen in 30% of patients with renal involvement (24). Rarer manifestations include focal segmental and focal proliferative glomerulonephritis (24). There is surprisingly little documentation of treatment-related nephrotoxicity, as one might expect in a disease treated primarily with nonsteroidal anti-inflammatory drugs (NSAIDs) as first-line therapy.

Accidents and violence

One of the interesting observations to emerge from the published studies of mortality in AS was the apparent increased rate of death by violent means, including accidental deaths and suicides. Radford and colleagues found 8 of 146 deaths were attributable to falls or suicide, almost twice the expected rate for the normal population (standardized mortality ratio 1.8) (5). Two studies in Finland have confirmed an increased incidence of violent deaths in AS patients, and suggested a link to alcohol use (alcohol use being somewhat higher in Finland than in other countries). Sixteen of the 152 deaths seen in the first cohort study were attributable to accidents or violence (SMR 1.4), and of these 8 were deemed to be alcohol-related, including 2 accidents, 2 suicides, 2 suffocations from vomit aspiration, and 2 alcohol poisonings (10). A subsequent study in 1989 examined alcohol-related deaths specifically, indicating 16 deaths due to accidents and violence, with 8 related to alcohol use (relative risk 2.64) among 71 deaths in AS patients (27). These results suggest a complex effect of the disease itself on AS patients, in particular regard to psychological coping mechanisms and possible self-medication with alcohol in the absence of effective symptomatic treatments. There is a need for a holistic approach to our care of AS (and all) patients, who may be at high risk of depressive disorders and substance abuse. Psychological evaluation and counseling may be indicated in many patients.

Iatrogenic mortality

Complications of therapy, although not specific to AS, are also important to consider, as they should be the most readily predicted and therefore prevented. Early studies indicated that radiation therapy, given for decades for spinal pain and stiffness in AS patients, caused significant increases in deaths due to aplastic anaemia, lymphoma and leukaemia (28-30). Radium-224 was also used historically in Europe with some benefit in AS, but was linked to the development of bone tumors (31), mammary cancers (32), and leukaemias (33). Radioactive therapies are no longer in use for AS.

The armamentarium of symptom-modifying and disease-modifying anti-rheumatic drugs (DMARDs) also may be associated with recognized side-effect profiles and potential complications. It is encouraging that the published mortality data do not reflect a large number of drug-related deaths, with very few cases of analgesic nephropathy or acute gastrointestinal bleeding as might be expected from NSAIDs. Prednisolone, sulfasalazine and methotrexate have been frequently used in AS although their effectiveness has been questioned (34). Anti-tumor necrosis factor therapies have taken centre stage in the management of AS in recent years, and to date have not been shown to cause an excess mortality in randomized controlled trials although there remains a lack of long-term follow-up data.

Conclusion

AS imparts an increased risk of death compared to the normal population. A number of potentially modifiable factors have been identified, highlighting the importance of timely cardiovascular risk management and attention to psychological health in our AS patients. Larger, longer-term studies are required to clarify many of these issues. Many countries now have their own AS patient registries, generally as a means of monitoring the effects of biological therapies in AS. Another obvious advantage is that, with time, more extensive, prospective data will be available than in the past regarding mortality and potential contributing factors. Data collection has been addressed by the Assessment of Spondyloarthritis International Society (ASAS), and a standardized core set of outcomes recommended for use in these registries to allow comprehensive data analysis and comparison between populations (35). These projects will hopefully allow us to answer some of the remaining questions regarding increased mortality rates in AS patients, and what we need to do to change that.

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