Mortality, course of disease and prognosis of patients with ankylosing spondylitis

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ABSTRACT

Patients with ankylosing spondylitis (AS) have about a 50% increased risk of mortality on the basis of the limited amount of data available. There is some evidence that the progression of disease is strongest in the first 10 years of disease but it is also clear that the disease keeps on being active for further decades. The overall burden of disease is similar to rheumatoid arthritis but the overall disease duration of AS is longer.

Prognostic factors have also not been studied extensively in AS but it seems clear that early hip involvement indicates a worse outcome. The same is true for early limitation of spinal mobility, laboratory evidence of ongoing disease activity (ESR, hypergammaglobulinemia), peripheral arthritis and dactylitis. The significance of organ involvement for the prognosis, especially in the kidney in the form of amyloidosis, and in the heart and lungs, is less clear.

Radiation therapy of the spine, which had been performed quite extensively in former decades, has been associated with a mean radiation dose of about double that of atomic bomb survivors and an increased risk of leukemia and mortality. This therapy has been largely abandoned nowadays. Elder rheumatologists report however that the clinical improvement of irradiated patients has been partly impressive.

Introduction

Ankylosing spondylitis (AS) is a frequent (1-3) inflammatory rheumatic disease which affects the spine severely in many young patients. The disease may lead to definite spinal restriction, impaired function, considerable handicap and a poor quality of life (4). The burden of disease was found to be similar to rheumatoid arthritis (RA) (5) – a disease with elevated mortality rates as shown by one of us many years ago (6).

However, a direct comparison between RA and AS is difficult since it is the back rather than the hands which is the primary site of difficulty and may not be recognized by health professionals in the early stages. Furthermore, AS usually starts considerably earlier in life, in the 3rd decade, which means that the total burden of disease lasts longer. Absence from work and work disability is clearly increased in AS patients compared to the normal population (7-9). In a recent survey in the US (10) the most prevalent quality of life concerns of AS patients included stiffness (90.2%), pain (83.1%), fatigue (62.4%) and poor sleep (54.1%). Taken together, the overall burden of disease in AS is considerable in most patients.

The therapeutic options to treat severely affected patients with AS have been very limited until recently, when infliximab (11,12) and etanercept (13) were found to be very effective to reduce signs and symptoms.

The availability of effective but expensive new therapies leads to a requirement for better descriptions of patient status to identify suitable candidates, including better description of prognostic variables for poor outcomes such as disability and death. This paper reviews the currently available knowledge concerning these matters.

Course of disease and prognosis

Two studies on outcome in AS have indicated that most loss of function and damage occurs during the first ten years of disease in patients with severe involvement (14, 15). However, a mean of 5-7 years is the period to make a diagnosis of AS according to recent reports from large databases (5, 16). Therefore, disease is diagnosed far too late in many patients. The more severely affected patients include about a

third of the total AS population (5), which is often already compromised when the diagnosis is made.

The outcome of adult-onset primary AS was studied in 100 patients in Norway (14). After a mean disease duration of 16 years, only 51.5% of the patients were still employed full-time. Cessation of work occurred at a mean disease duration of 15.6 yr, and was associated significantly with female sex, low levels of education, acute anterior uveitis, development of a 'bamboo spine' and the co-existence of non-rheumatic diseases. Functional status, evaluated by analysing capacity to perform activities of daily living, revealed similar results in male and female patients. Most of the loss of function occurred during the first 10 years of disease, and was correlated significantly with peripheral arthritis and spinal radiographic changes. After more than 20 years of disease, more than 80% of the patients still complained of daily pain and stiffness, and more than 60% reported daily use of drugs (14).

In the US, 150 war veterans with AS were entered into a prospective study in 1947 (15). In 1957, 142 were traced and then reviewed periodically. In 1980, 81 AS patients were still alive. Information was obtained from 67 (83%) of the survivors and 51 with a mean disease duration of 38 years were reexamined. Of these, 47 were functioning well (92% of those examined, 31% of the original cohort). However, the disease had progressed to cause severe spinal restriction in 21 (41% of those examined), of whom 12 had peripheral joint involvement early in their course and 9 had iritis. Seventy-four percent of the examined patients who had mild spinal restriction after 10 years did not progress further, while 81% of the patients who had severe spinal restriction in 1980 were severely restricted within the first 10 years. An important observation was that hips which remained normal after 10 years of disease did not become diseased subsequently (15).

Taken together, both studies emphasize that definite damage due to early progression of the disease occurs during the first ten years after disease onset.

The significance of hip involvement in AS patients was recently assessed in a cross sectional study from the U.K. (17) by measuring change in 2,284 radiographs of 571 AS patients which were scored retrospectively using the Bath Ankylosing Spondylitis Radiology Index (18). The rate of radiological progression was calculated using longitudinal data of two sets of 54 radiographs taken 10 years apart. Progression to cervical spine disease was associated with: longer disease duration, severity of hip and lumbar involvement, and a history of iritis ($p < 0.001$). Lumbar involvement was associated with longer disease duration, older age, and severity of cervical and hip involvement ($p < 0.001$). Hip involvement, associated with a longer disease duration ($p < 0.001$), was identified as an indicator of cervical disease. Longitudinal analysis of these patients indicated marked variation among patients, with a rather slow mean rate of progression. Also, the progression of AS over any 10 year period was linear [first 10 years = 30% (SD 0.3) of potential change, 10-20 yrs = 40% (SD 0.3) change, 20-30 yrs = 35% (SD 0.4) change ($p = 0.5$)]. The authors concluded that AS is a linearly progressive disease with about 35% change every 10 years with no indication of more rapid progression during the first 10 years. Similarly, spinal involvement is largely an expression of disease duration, while hip involvement, which is seen in about 25% of the patients, may predict a more severe outcome for the cervical spine.

Thus, this retrospective study suggests that AS runs a continously progressing course with no major differences between the first and later decades, unlike other studies. Possibly the design of the study and patient selection might have influenced these results. The authors of this study have recently proposed a radiograph scoring method for the standardized assessment of hip involvement in AS (19).

The significance of hip involvement was also emphasized in two French studies (20, 21). In the first study, 328 patients diagnosed as SpA on the basis of the ESSG criteria (18) were monitored by a single observer. Long-term outcomes of the 151 patients who had followup of 10 or more years were classified on a 3-point-scale. Progression was classified as minor in 81 patients (53.6%), moderate in 42 (27.8%) and severe in 28 patients (18.5%). Seven of 12 candidate predictive factors during the first 2 years of the disease, collected by history at the time of the first visit, were correlated significantly with disease severity (odds ratio; CI 95%); hip arthritis (22.9; 4.4 - 118); erythrocyte sedimentation rate (ESR) > 30 mm/h (7; 4.8 - 9.5); poor efficacy of nonsteroidal antiinflammatory drugs (8.3; 2.6 - 27.1); limitation of lumbar spine (7; 2 - 25); sausage-like finger or toe (8.5; 1.5 - 9); oligoarthritis (4.3; 1.4 - 13.1); onset ≤ 16 years (3.5; 1.1 - 12.8). If none of these factors was present at entry, a mild outcome could be predicted (sensitivity: 93%; specificity: 78%). If a hip was involved, or if 3 factors were present, a severe outcome was likely (sensitivity: 50%) and mild disease progression virtually excluded (specificity: 98%). From this study, it appears that predictive factors of poor or benign longterm outcome can be defined early after onset in most patients with SpA.

Hip involvement, which may be used as a marker of disease severity, is more frequent in SpA developing in North Africa. In a retrospective, cross-sectional, multicentre study, performed in collaboration with French rheumatologists, the predisposing factors for hip involvement were determined in 518 North African SpA patients (21). The risk of hip involvement was estimated at 39+/-3% after 10 years disease duration. The factors identified using Kaplan-Meier curves and uni- and multivariate Cox proportional hazard models were: diagnostic delay less than 7 years, age at onset below 24 years, and a combination of 'lower social class'and 'no refrigerator at home'. The authors concluded that both genetic and environmental factors appear to influence the severity of SpA.

An attempt to clarify genetic and environmental influences on the severity of AS was recently undertaken in a study from the U.K. (22). Overall, 173 families with more than one AS case were recruited, including 384 affected indi-

viduals (120 affected sibling pairs, 26 affected parent-child pairs, 20 families with both first- and second-degree relatives affected, and 7 families with only second-degree relatives affected). Both disease activity as assessed by the Bath Ankylosing Spondylitis disease activity index (BASDAI) (23) and functional capacity assessed by the Bath Ankylosing Spondylitis functional index (BASFI) (24) were found to be highly familial (BASDAI familiality 0.51 [$P = 10^{-4}$], BASFI familiality 0.68 [$P = 3 \times 10^{-7}$]). No significant shared environmental component was demonstrated to be associated with either the BASDAI or the BASFI. Inclusion of age at disease onset and duration of disease as covariates made no difference in the heritability assessments. A strong correlation was noted between the BASDAI and the BASFI (genetic correlation 0.9), suggesting the presence of shared determinants of these two measures of activity and functional capacity. However, there was significant residual heritability for each measure independent of the other (BASFI residual heritability 0.48, BASDAI 0.36), perhaps indicating that not all genes influencing disease activity influence chronicity. Age at disease onset was not statistically significant (heritability 0.18; P = 0.2). Segregation studies suggested the presence of a single major gene influencing the BASDAI and the BASFI. This study demonstrates a major genetic contribution to disease severity in patients with AS. The authors concluded that, similar to susceptibility to AS, shared environmental factors seem to play a minor role in determining the disease severity.

Mortality studies in non-radiated AS patients

The largest published study of age-specific mortality rates in AS was published in 1977 (25). The mortality of 836 AS patients, diagnosed during 1935-57 who, importantly, had not received deep radiation therapy, was assessed. The follow-up observation (up to January 1, 1968) was more than 13 years from enrollment. Men had higher mortality rates than women, as seen in the general population. Excess mortality was observed in men who had comorbid diseases known to be associated with spondylitis, such as ulcerative colitis, nephritis and tuberculosis or other respiratory disease. The mortality risk relative to the general male population was fourfold for all gastrointestinal diseases, nearly two-fold for accidents, suicide and cerebrovascular disease and 40% in excess for other circulatory diseases. These results indicated that, at least in men,AS has life-threatening consequences related to several organ systems.

In a study by Khan *et al*. a life-table analysis of survival was performed retrospectively on 56 white, mainly male (n = 49) AS patients (26). The disease was diagnosed between 1934 and 1960 at a mean age of 35.2 years and patients were monitored until December 1975, indicating a mean duration of 22 years. The expected survival was calculated from life-tables for the US population matched for sex, age, race, geographic area, and calendar year. For the first 10 years of follow-up, there was no difference in the observed and expected survival. By 20 yr after diagnosis, 37 patients were observed to have survived vs. 46 expected ($p = 0.001$). By 40 years after diagnosis, 16 were observed to have survived vs. 21 expected ($p = 0.063$). Taken together, this small study also indicated increased mortality of AS patients. For all of these studies, the possibility of selection bias needs to be mentioned. Thus, the increased mortality rated reported may only apply to the more severely affected patients.

Trends in the incidence, clinical presentation and survival of AS patients diagnosed between 1935 and 1973 (27) and 1989 were examined in a population-based descriptive study among residents of Rochester, Minnesota, US (28). In 102 AS patients diagnosed from 1935 through 1973, no significant change was seen in the incidence over the 39 years (27). Three times as many males as females were affected. In contrast to another recent report, survivorship of males with AS was not different from that of the general population, whereas survivorship of females with AS was reduced. The overall prevalence was 129/100,000.

In a second study from the Mayo Clinic (28) an overall age- and sex-adjusted incidence rate of 7.3 per 100,000 person-years (95% CI: 6.1 - 8.4) was reported. Overall survival was not decreased up to 28 years following diagnosis. It should be noted that population-based studies in Rochester Minnesota of mortality in RA also did not show any increases vs. the general population, suggesting that detection of mild cases in this socio-economically advantaged region may identify different patients than are seen in most clincial settings.

In an early study from Finland (29) 76 patients treated for AS at a big hospital during the 1950s were re-examined after a mean disease duration of 30 years. Using limited epidemiologic techniques, the prognosis of AS in that study was found to be relatively good. A further analysis of this dataset was directed to mortality and causes of death in 64 AS patients (30). Hypergammaglobulinaemia (HG) was found in 18 patients. A total of 36 deaths occurred during the follow-up time, 13 in the HG group and 23 in the non-HG control group. Death from uraemia caused by renal amyloidosis was noted in 6 patients in the HG group and 3 in the non-HG group ($p < 0.01$). Therefore, HG was indicating a poor prognosis in these patients.

The causes of death of 79 AS patients diagnosed between 1952-59 were investigated by the same author (31). The most common cause of death was cardiovascular disease in 35.4% of the patients, while AS itself was reported to be the cause in 29.1%, violent death in 10.1%, malignancy in 8.9%, gastrointestinal diseases in 6.3%, pulmonary tuberculosis in 2.5%, urogenital diseases in 2.5%, respiratory diseases in 3.8% and diabetes mellitus in 1.3%. Only one patient had a lymphoma and another patient chronic lymphatic leukaemia despite the fact that almost every patient had received radiation therapy (see below). Of note, uraemia caused by renal amyloidosis was the immediate cause of death in 18% of the cases and a contributory factor in 3.8%. Uraemia caused by renal amyloidosis appeared as a cause of death in Finnish

RA patients at a much higher rate than in any other country, with similar trends in AS, although the overall incidence of amyloidosis in Finland appears to be declining.

The same author examined mortality and causes of death in an even larger cohort of 398 AS patients (47 women, 351 men), admitted to hospital for the first time between 1961 and 1969 (32). The mean age at first admission was 36.5 years. After a mean follow up time of 25 years, a total of 152 patients (12 women, 140 men) had died vs. 103 expected (9.4 women and 93.7 men) indicating an overall mortality 1.5 times higher than expected in AS patients. Patients who had died were significantly older, had a higher ESR, and more inflamed peripheral joints when first seen than the surviving patients. The primary difference between the observed and expected causes of death was the high incidence of deaths from AS, which was the underlying cause of death in 27 patients. The mechanism of death in these patients was secondary amyloidosis in 19, cardiovascular complications in 6 and fracture of the spine in one. Excess deaths due to circulatory, gastrointestinal and renal diseases, and violence were also observed.

The latter was confirmed in a later study from Finland (33) in which AS patients were found to have an increased incidence of deaths from accidents and violence. The study covered all 71 subjects (58 men, 13 women) who had died in Finland in 1989 and who were entitled under the nationwide sickness insurance scheme to receive specially reimbursed medication for AS. Furthermore, the death certificates of an earlier cohort study concerning mortality in AS were re-examined: 16 subjects (14 men, 2 women) in the 1989 mortality series had died of accidents and violence, 9 deaths (3 accidents, 2 suicides and 4 cases of alcohol poisoning) were alcohol related. The RR of such deaths in subjects with AS compared to the Finnish population was 2.64 (95% CI: 1.4 - 4.8). In the cohort study, 16 deaths due to accidents, alcohol, and violence had been observed versus 11.4 expected. The authors concluded that uncontrolled use of alcohol is an important determinant of deaths from accidents and violence in Finnish AS patients. In addition, the authors speculated that the vulnerability of the inflamed and osteoporotic spine of AS patients may well lead to a higher incidence of fractures.

Spinal injuries in AS patients were reviewed retrospectively by Graham *et al*. from the surgical point of view (34). Importantly, fractures occurred frequently as a result of minimal trauma and were associated with severe neurologic deficits in 75% of cases. A characteristic fracture pattern was seen radiographically, which appeared to result from the altered biomechanics of the ankylosed spine. Although the fractures were markedly unstable, non-operative treatment was reported to be uniformly successful in achieving union. The incidence of complications and the mortality of these patients was lower than that reported in other studies. This success was attributed to the solid conservative management within a spinal cord injury unit.

An increased risk of fractures (35-37) and a low bone density (38-40) most probably related to inflammation present already in early disease stages, has been reported by several groups. Unfortunately, no studies on specific treatment of this clinical problem are available.

Several studies indicate that the heart is involved significantly in patients with AS. This is true for the aortic valves, the conduction system and the myocardium itsself (41). After it was reported that an HLA B27-associated inflammatory disease process may be the underlying cause in 15-20% of men with permanent pacemakers (42), a study indicated no influence on mortality associated with HLA B27 or with HLA B27-associated rheumatic disorders (43). It is not clear whether AS patients have an increased risk of ischaemic heart disease as reported in other inflammatory rheumatic diseases.

Mortality in irradiated AS patients

After increased mortality after radiation therapy in AS patients was reported in 1965 (44), several studies of the same cohort of AS patients from England and Wales, were published which all agreed that there was an increased mortality of AS patients due to radiotherapy.

Mortality up to 1 January 1983 has been studied in 14,106 AS patients given a single course of X-ray treatment during 1935-54 (45). For neoplasms other than leukaemia or colon cancer, mortality was 28% greater than that of the general population of England and Wales. This increase was interpreted as being likely a direct consequence of treatment. The proportional increase reached a maximum of 71% between 10.0 and 12.4 years after irradiation and then declined. There was only a 7% increase in mortality from these tumours more than 25.0 years after irradiation and the relative risk was significantly raised only for cancer of the oesophagus in this period. For leukaemia there was a threefold increase in mortality that is also likely to have been due to the radiotherapy. The relative risk was at its highest between 2.5 and 4.9 years after the treatment and then declined, but the increase did not disappear completely, and the risk remained nearly twice that of the general population more than 25.0 years after treatment. For colon cancer, which is associated with spondylitis through a common association with ulcerative colitis, mortality was increased by 30%. For non-neoplastic conditions there was a 51% increase in mortality that was thought to be associated with the disease itself rather than its treatment.

In the same cohort, mortality was studied in 14,111 AS patients given a single course of x-ray treatment during 1935-54 (46). Mortality from all causes combined was 66% greater than that of members of the general population. There were substantial excesses of deaths from non-neoplastic conditions. Again, these appeared to be associated with the disease itself rather than its treatment. However, a nearly fivefold excess of deaths from leukaemia, and a 62% excess of deaths from cancers of sites that would have been in the radiation fields ("heavily irradiated sites"), were likely to have been a direct consequence of the radiation treatment itself. The excess death rate from leukaemia

was greatest 3 - 5 years after treatment and was close to zero after 18 years. In contrast, the excess of cancers at heavily irradiated sites did not become apparent until nine or more years after irradiation and continued for a further 11 years.

The risk of a radiation-induced leukaemia or other cancer was related to the age of the patient at the time of treatment. Those irradiated when aged 55 years or more had an excess death rate from leukaemia more than 15 times that of those treated under 25 years of age, and a similar difference was apparent for cancers of heavily irradiated sites. It was calculated that using low radiation doses about two deaths from leukaemia would be induced per million people per rad of x-rays per year for up to 20 years after exposure. Because of the failure to find a clear dose-response relationship, this estimate must be regarded with caution, but it is in reasonable agreement with studies on atomic bomb survivors (see below).

In another study with the same cohort of 15,577 AS patients diagnosed between 1935 and 1957 in the UK, of whom 14,556 received X-ray treatment, it was found that by January 1992 over half of the cohort had died (47). Among the irradiated patients, cancer mortality was significantly greater than expected from national rates for the U.K., with a ratio of observed deaths to expected RR = 1.3, and significant increases individually for leukaemia, non-Hodgkin's lymphoma, multiple myeloma and cancers of the oesophagus, colon, pancreas, lung, bones, connective and soft tissue, prostate, bladder and kidney. Unexpectedly, among the non-irradiated patients, cancer mortality was lower than expected from national rates (RR = 0.79). Among irradiated patients, the RRs for leukaemia, lung cancer, and all other neoplasms all decreased significantly with increasing time since first treatment following an initial increase. By 35 years after first treatment, the radiation-related excess for lung cancer had completely disappeared, while the RR remained higher for other neoplasms, although at a lower level than in earlier periods.

Most irradiated patients had received several courses of treatment within 5 years. The mean total body dose received in this period was 2.64 Gy, with the heaviest dose to the vertebrae. There was a linear dose response for all neoplasms except leukaemia with an excess RR of 0.18 Gy-1 in the period 5 - 25 years after first treatment.

Leukemia mortality was studied further in this cohort of 14,767 adult AS patients, of whom 13,914 patients received X-ray treatment (48). Most irradiated patients received all their exposure within a year. The mean total marrow dose was 4.38 Gy. Doses were non-uniform, with heaviest doses to the lower spine. By January 1992, there were 60 leukemia deaths among the irradiated patients, almost treble that expected from national rates, while leukemia mortality was not increased among non-irradiated patients. Among those irradiated, the ratio of observed to expected deaths from leukemias other than chronic lymphocytic leukemia was greatest in the period 1-5 years after the first treatment (RR = 11, 95% CI: 5.3 - 21), then decreasing to 1.9 (95% CI: 0.9 - 3.4) in the 25 year period. There was no significant variation in this ratio with sex or age at first treatment. The ratio for chronic lymphocytic leukemia was slightly but not significantly raised (ratio = 1.44, 95% CI: 0.6 - 2.8). Ten years after first exposure, the linear component of excess RR was 12.4 per Gy (95% CI: 2.3 - 52.1). The average predicted RR in the period 1-25 years after exposure to a uniform dose of 1 Gy was calculated to be 7.

Radiation-induced cancer mortality rates among atomic bomb survivors with doses of at least 100 rad and AS patients given X-ray therapy have been compared by Darby *et al.* (49). Of note, the estimated average mean bone marrow dose for the spondylitics was more than twice that for atomic bomb survivors, and yet AS patients experienced only half the risk of radiation-induced leukemia of atomic bomb survivors. For sites that were heavily irradiated in the spondylitics, provisional estimates indicate comparable doses in the two studies, and similar levels of cancer risk were observed. For these sites, when information from the studies was combined, there were statistically significant excesses for cancers of the esophagus, stomach, lung, and ovaries, multiple myeloma, other lymphomas, and tumors of the spinal cord and nerves. Very high RRs for tumors of the spinal cord and nerves were observed in both studies.

The dose-response relationship for radiation-induced leukemia was also examined in a pooled analysis of 3 exposed populations (50): Japanese atomic bomb survivors, women treated for cervical cancer, and irradiated AS patients. A total of 383 leukemias were observed among 283,139 study subjects. Considering all leukemias apart from chronic lymphocytic leukemia, the optimal RR model had a dose response with a purely quadratic term representing induction and an exponential term consistent with cell sterilization at high doses. Again, the RR decreased with increasing time after exposure and increasing attained age. Taken together, radiation therapy for AS patients has been abandoned due to the increased incidence of leukemias

Radium chloride therapy has recently been approved for AS in Germany mainly on the basis of many positive open studies performed in earlier decades. However, controlled data are scarce.

Mainly between 1945 and 1955, several thousand German patients with AS, tuberculosis and a few other diseases have received multiple injections of the short-lived alpha-particle emitter radium-224. Many open studies reported significant benefit of such treatment for AS patients (51). To assess the safety of this therapy the German Institute of Radiobiology in Munich has performed several follow up studies, two of which are presented here (52, 53).

The majority of 1577 AS patients from 9 German hospitals treated with multiple injections of (224)Ra in the years 1948-1975 received one series of 10 weekly intravenous injections of about 1 MBq of (224)Ra each (52).This dose leading to a mean absorbed dose due to alpha-particle radiation of 0.56 Gy to the marrow-free skeleton of a 70 kg male (mean bone surface dose of about

5 Gy). A control group of 1462 AS patients with roughly the same age distribution was followed up in parallel. By the end of 1998, 649 patients in the exposed group and 762 control patients had died. Among other observations, it is of particular interest that 13 cases of leukemia in the exposed group were observed. Although this represents a highly significant excess ($P < 0.001$) compared to a standard population, there was only a marginally significant excess in comparison to the 7 cases observed in the control group. Subclassification of the leukemias shows a clear preponderance of the myeloid leukemias in the exposed group (8 cases observed compared to 1.7 cases expected, $P < 0.001$), whereas in the control group the observed cases are within the expected range for myeloid leukemia (3 cases observed compared to 2.2 cases expected, $p = 0.3$). Four cases of malignant tumors in the skeleton had been observed until then.

Taken together, it is not clear why so many patients in the control group died but a very small risk of myeloid leukemia in patients treated with radiumchloride cannot be excluded.

In another study of 899 AS patients treated in the early 1950s most of the high-dose patients and nearly all of those treated as children or juveniles (< 21 years of age) were included and followed up (53). In this study cohort, 56 malignant bone tumors occurred in a temporal wave that peaked 8 years after exposure, whereas less than one case would have been expected during follow-up period. Most of the malignant bone tumors were osteosarcomas and fibrous-histiocytic sarcomas. Taking advantage of a new improved dosimetry system, a re-analysis of the data now performed resulted in modified bone surface doses, especially for those treated at younger ages. A significant increase in bone tumor risk is now demonstrated in patients treated at young age and in those with treated with high doses of the compound. Taken together, only patients > 30 years or older should be treated with doses < 10 MBq, and controlled studies should be performed to demonstrate the efficacy and safety of radiumchloride in AS.

Conclusion

There is no commonly agreed set of variables for the assessment of long-term outcome of AS patients. Permanent pain, ongoing disease activity, disease manifestations in hips, peripheral joints, entheses, the uvea and the heart, limitation of spinal mobility, loss of function, osteoporosis including fractures, radiographic damage and development of amyloidosis are possible candidates. On the basis of the limited available data, predictors of a bad outcome, such as hip involvement and limited spinal mobility are outcome parameters as well. Disease progression leading to damage and loss of function seems to be most rapid during the first 10 years of disease. This may augment the problems arising from the known diagnostic delay of at least 5 years. An elevated ESR and hypergammaglobulinemia as possible indicators of active disease may predict a bad course of disease. There is reason to think that the severity of AS is genetically determined, similar to the susceptibility. AS is associated with an inferior quality of life and early withdrawal from gainful employment.

The existing set of data on mortality in AS suggests that there is an increased mortality in AS which is independent from radiation therapy – a treatment which is clearly associated with an increased risk of leukemia and some forms of cancer, relatively more than people who were exposed to the atomic bomb. The increase in mortality may well be in the order of a 50% increase, corresponding to a relative risk of 1.5 as found in a Finnish study. The finding that there were many deaths related to alcohol, violence and trauma suggests a possible national influence but may also indicate a greater vulnerability of the spine in AS, as a result of inflammation and osteoporosis. Our knowledge about the significance of cardiac involvement and mortality in AS remains rather limited. Renal amyloidosis in AS leads to permanent dialysis and premature death. It can be concluded that at least a third of the patients with ankylosing spondylitis have a severe course of disease and a reduced life expectancy.

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