Differences and similarities between ankylosing spondylitis and rheumatoid arthritis: epidemiology

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ABSTRACT

Ankylosing spondylitis (AS) and rheumatoid arthritis (RA) are among the most common rheumatic diseases. The epidemiology of these diseases highlights both similarities and differences. Prevalence rates of approximately 0.2–1% have been reported for the diseases, but the rate for AS is increasing while RA is declining. Geographical variations exist in the incidence and prevalence of the diseases, although the majority of studies have been conducted in northern Europe and North America. AS is a predominantly a male disorder, whereas more females are affected by RA. Both diseases result in increased disability, reduced work productivity, and increased mortality rates. These similarities and differences may give us important clues as to the aetiology of both diseases.

Introduction

Ankylosing spondylitis (AS) and rheumatoid arthritis (RA) are among the most common inflammatory joint diseases in adults which frequently result in physical limitation, work disability and increased mortality rates. This article presents a systematic comparison of the epidemiology of these two common rheumatic diseases, summarised in Table I.

Prevalence and geographic variations

Similar prevalence rates have been reported for both RA and AS, with rates of 0.5–1% for RA (1) and 0.2–1.2% for AS (2). While the majority of studies of prevalence have been conducted in northern Europe and North America, with a few reports in developing countries, some regional differences in prevalence have been identified. Higher prevalence rates of both RA and AS have been reported in northern Europe and North America than in southern Europe and developing countries (3-11). These differences may be a result of different age structures and genetic profiles in different regions. In addition, environmental and lifestyle factors may contribute to the different profiles, and dietary factors such as olive oil, fish consumption and the Mediterranean diet, may offer a protective effect for disease development and disease severity.

Prior to the use of MRI to assess changes, significant delays in the diagnosis of AS may have occurred as radiographic changes traditionally required for a diagnosis of AS occur as late as five to nine years after the onset of clinical symptoms. This may lead to potentially inaccurate estimates of incidence and prevalence of the disease reported in earlier studies.

Incidence and geographic variations

Generally, incidence rates of 0.5–8.2 per 100,000 population per year have been described for AS (2) and for RA incidence rates of 20–300 per 100,000 population per year have been reported (1).

For both AS and RA, there are limited data on the incidence of the diseases, with most studies being conducted in northern Europe and North America. A similar pattern for both diseases is seen, with higher rates in northern Europe than in southern Europe.

Trends in prevalence

Data on trends in the incidence and prevalence of RA and AS are limited, complicated by the different methodologies and criteria used to identify cases over time. In Norway, the estimated point prevalence of AS rose from 0.036% in 1970 to 0.10% in 1980 and to 0.21% in 1990 with a period prevalence of 0.26% (12). A decline in the prevalence of RA has been shown

Table I. Epidemiology of AS and RA.

	Ankylosing spondylitis	Rheumatoid arthritis
Prevalence (Overall rate)	0.2 – 1.2% (2)	0.3 – 1% (1, 3, 19)
Incidence	0.5 – 8.2 per 100,000 population (2)	20–300 per 100,000 population (1) 0.1–0.5 per 1,000 population (3)
Geographic variations	NORTHERN EUROPE & NORTH AMERICA Prevalence: 0.1 1.8%; (4-11) Incidence: 3 – 10 per 100,000 (9, 12, 32, 52, 88)	NORTHERN EUROPE & NORTH AMERICA Prevalence: 0.5 – 1.1% (3, 45) Incidence 2–7 per 100,000 (3)
	SOUTHERN EUROPE Prevalence: 0.24 – 1.6 (35) Incidence: 1.5 per 100,000 (37)	SOUTHERN EUROPE Prevalence: 0.2 – 0.7% (3, 45) Incidence: 1–2 per 100,000 (3)
	SOUTH AMERICA Prevalence: No data Incidence: No data	SOUTH AMERICA: Prevalence 0.01 – 0.05% (3) Incidence – No data
	ASIA Prevalence: 0.02 – 0.54% (89-94) Incidence:0.48 per 100,000	ASIA: Prevalence: 0.3 – 0.4% (3) Incidence: 3–9 per 100,000 (3)
	MIDDLE EAST Prevalence: 0.12 – 0.49% (95, 96) Incidence: No data	MIDDLE EAST: Prevalence: 2 – 5 per 100,000 (3) Incidence: No data
	AFRICA Prevalence: No data Incidence: No data	AFRICA: Prevalence: 0 – 4 .5 (females) (45) Incidence: No data
Trends in above	PREVALENCE Increasing (12) 0.036% in 1970, 0.10% in 1980, 0.21% in 1990	PREVALENCE Declining (16, 21) Over a 25 year period declined by 29% in males and 40% in females
	INCIDENCE Stable (12, 17, 18) Slightly declining in USA, Stable in Norway	INCIDENCE: Declining (19). 1955–1964: 61.2 per 100,000; 1985–1994: 32.7 per 100,000
Global Missing Data/Gaps	Little/no data for most of Asia, Australasia, Caribbean, Central and Eastern Europe, Latin America, Oceania, Sub-Saharan Africa	Most incidence and prevalence studies have been done in Northern European and North American countries.
Mean age of onset	Adult onset: 20 – 30 years (24)	Two peaks: Younger onset 42 years, Older onset 68 years (26)
Gender M:F ratio	Males > Females (24, 33, 36-38) 1.2 – 9 : 1	Females > Males (40) 1: 2 – 3:1
Natural History	High disease activity in first 10 years (54); Radiographic changes required for diagnosis occur as late as 5 – 10 years after onset of clinical symptoms; Greater rate of disease progression in men than women (29); Extra-articular manifestations including peripheral arthritis, enthesitis, dactylitis, uveitis, and inflammatory bowel disease (54, 57).	Progressive disease. Radiographic progression and severe function decline over 10 years (53). By 5 years, most patients experience some difficulties in activities of daily living. Early treatment results in a better outcome. Extra-articular features include rheumatoid nodules, secondary Sjögren's syndrome, and pulmonary fibrosis (58).
Case Fatality	Mortality rates 1.5 times higher than general population (80, 97); Over 50% due to respiratory complications (78); 30% as a consequence of spinal fractures, 18% within 3 months after fractures (98).	Mortality rates 1.5 – 1.6 higher than general population (45); Acute attributable cause of death similar to general population, with cardiovascular disease most common; infection and pulmonary disease as causes of death are higher than in general population (76).
Remission	Rates of partial remission after TNF-a antagonist treatment ranged from 0% to 31% (82); 20% improved while pregnant but disease flare-up during first 3 months postpartum (83).	Natural remission rates, ie with no DMARD treatment, of 9.5 – 14%; (81); Remission rates of 31-56% with combinations of DMARDs and TNF inhibitors (81).
Risk Factors	INFECTIOUS AGENTS: Klebsiella pneumoniae implicated as a triggering and/or perpetuating factor in the aetiopathogenesis of ankylosing spondylitis (48, 86).	SMOKING: RR 1.43-3.8 for current smokers; 1.47-2.6 for past smokers; (84, 85, 99, 100); OBESITY: BMI ≥30 associated with OR of 3.74 for developing RA (85); BLOOD TRANSFUSION: RA associated with history of blood transfusion (OR 4.83) (85); FEMALE SEX HORMONES: Oral contraceptive pill may protect against the development of RA; RA is rare during pregnancy and is more common in nulliparous women (1).
Genetics	Highly heritable, with >90% of the risk of developing the disease determined genetically (101); Twin pairs with HLA-B27-positive indicated that additive genetic effects accounted for 94% of the variance in the disease causation (52); Strongly associated in Caucasians, most Asians and Middle Eastern; Not strongly associated in Africans (10, 47, 48, 102, 103).	Heritability 65% in Finish population, 53% in UK (41); Twin studies- pairwise concordance percentage for RA was 12.3 in monozygotic twins and 3.5 in dizygotic twins (43); Pairwise concordance percentages for RA in twins: MZ 21% (95% (CI = 6 to 44), DZ 0% (95% CI = 0 to 25) –genetic factors play some part in the aetiopathogenesis of RA but do not account entirely for its determination (44).

in recent years (13-15), particularly in women where a reduction of 31% was reported compared to 19% in men (15). However, it must be noted that the same methodology was not used in the two surveys that elicited the data. The prevalence of RA in Native Americans has also decreased in recent years (16) and while there is no clear explanation for this decline, it is possibly related to changing exposure to an environmental risk factor and/or a change in treatment rates (16). People in remission may not be detected as cases in population studies of prevalence, thus recent advances in treatment and combination drug therapies may contribute to the declining prevalence rates of RA.

Trends in incidence

The incidence and clinical presentation of AS have not changed significantly over the past few decades (17). In Minnesota, USA, between 1935 and 1989, a slight decline was seen in the overall age- and gender-adjusted incidence rate, but little change in the age at symptom onset or diagnosis was seen over the 55-year study period (18). In Norway, the incidence rate has remained relatively stable over a 34-year period (1960–1993) (12).

While the incidence of AS remains stable, a number of studies have shown that the incidence of RA is declining (19-22). An extensive study in Minnesota indicated an incidence rate of 61 per 100,000 population per year was seen between 1955 and 1964 declining to 32 per 100,000 in 1985 to 1994 (19). A similar decline has been reported in Finland (20). This reduction may be due to the impact of changes in lifestyle which reduces the presence of risk factors, such as obesity, in the community. However, a shift towards an increasing incidence of RA amongst the elderly has been shown in Finland (23) and with the aging population in Europe, North America, and Australia, an increase in incidence and prevalence of RA may be predicted during the next decade.

Age of onset

The diagnosis of AS occurs at an earlier age than RA. The mean age at onset of AS is reported to be approximately 22 years (24), with an onset after the age of 50 years being uncommon (25). In contrast, rheumatoid arthritis commonly appears later in life, with two identified peaks. The average ages of disease onset have been reported as 42.2±10.4 years in younger onset RA and 68.4±4.6 years in late onset RA (26). A mean age of onset of approximately 50 years has been reported in Caucasians (27).

Gender differences have been identified in the age of onset of RA. The peak age of onset for women is approximately 10 years younger than for men (28). In AS the average age at disease onset was similar for men and women (29). Racial differences in the age of onset of RA have also been identified (27), while several studies of AS have reported a similar age of onset across countries (30-35).

Gender

RA is a disease that affects more females than males, while AS is characterized by a male predominance. In the Caucasian population, AS has been reported to affect approximately 1% of men and 0.49% of women (36) with male to female ratios of 1.2–9:1 (24, 33, 37, 38). A review of gender differences in rheumatic disease has identified that female to male ratio for RA is 2-3:1 (39, 40).

Genetics

Both AS and RA are partially inherited diseases, with a stronger basis for heritability in AS than RA. Up to 98% of the population variance of AS is genetically determined and the heritability of RA has been reported to be 65% in a Finnish cohort and 53% in the UK (41). The influence of genetic factors in RA has been demonstrated in twin studies which have shown that if one member of a pair of identical twins has the disease, the other twin has a 15% chance of developing the disease (42). The pairwise concordance percentage for RA has been reported to be 12.3 to 21% in monozygotic (MZ) twins and 0 to 3.5% in dizygotic (DZ) twins (43, 44). The conclusion from this is that genetic factors play some part in the aetiopathogenesis of RA but cannot account entirely for its determination.

It is not clear whether genetic factors are related to the risk of RA, or to the severity of the disease, or both (45). One of the genetic components of seropositive RA has been mapped to a short gene sequence, the shared epitope (1) which appears to be the marker for RA disease severity rather than susceptibility. It has been suggested that the variations seen in the incidence and prevalence of RA among different populations or ethnic groups could partly be explained by genetic variation in the HLA region, and variation in the prevalence of the shared epitope in different populations (45).

The major genetic effect of AS arises from Human Leukocyte Antigen B*27 (HLA-B27) (46). The relationship between HLA-B27 and AS was discovered in 1973, which considerably differentiated the disease from RA (47). The prevalence of AS varies with the percentage of HLA-B27 positive individuals in different populations. AS is highly associated with HLA-B27 in Caucasian patients (10, 48). The antigen was found in more than 90% of patients with AS when compared to 8% or less of control populations (48-51). In a recent study of twins, the HLA-B27-positive twin pairs indicated that additive genetic effects accounted for 94% of the variance in the causation of AS (52). The finding added to the previous evidence of a major genetic effect in the pathogenesis of AS (52).

Natural history

Both AS and RA are progressive diseases (53). The greatest progression is seen in the first 10 years of both AS and RA show the greatest progression, but disease activity continues for further decades (53, 54). Approximately 1 in 5 AS patients report high disease activity (55) and most patients with an RA duration of 5 years or more experience some difficulties in most activities of daily living (56).

In addition to the characteristics of inflammatory back pain and diminished spinal mobility, AS is associated with a number of extra-spinal manifestations that contribute to disease burden, including peripheral arthritis, which is common in AS, enthesitis (inflammation at sites of tendinous or ligamentous

attachments to bone), dactylitis (sausage-shaped swelling of the fingers or toes), uveitis (inflammation of the uvea or middle layer of the eye), and inflammatory bowel disease. Patients with AS also report significant fatigue relative to the general population (54, 57).

Similarly, patients with RA often experience clinically important extra-articular disorders such as pericarditis, pleuritis, vasculitis, neuropathy, and ophthalmological manifestations (58). A study of extra-articular features reported that the most common features were rheumatoid nodules, secondary Sjögren's syndrome, and pulmonary fibrosis. Patients with extra-articular disease and other comorbidities experience poorer outcomes and higher mortality (58).

Several factors contribute to the course of RA (58). The extent and severity of inflammatory changes in the joints varies and depends on the factors caused by both the disease itself and the impact of anti-rheumatic drugs. RA also has an impact on the general health of a person with the disease, including both extra-articular disease and associated comorbidities. The combination of these different aspects of RA causes disability and reduces quality of life. The overall natural history of RA remains complex and therefore its different components should be described independently (58).

Disability

AS and RA are associated with severe disability and major disruptions to activities of daily living. About 1 in 4 people with AS report severe pain (55) and more than half report problems with daily activities, including sleeping, driving, shopping, and having energy for social activities (59). Fatigue is a significant problem in 63-76.5% of patients with AS (60-62) and over 80% of people with RA (63). After pain, fatigue is the symptom most frequently reported by people with RA (64).

In both AS and RA, higher levels of disease activity have been associated with greater disability. Female AS patients have reported higher levels of disease activity and more physical limitations than male patients (65). Disease activity and reduced mobility result in more activity and participation restrictions in female than in male patients. As in AS, physical disability has been reported to be significantly worse in female RA patients and also older patients with RA (66). A study of the factors associated with functional disability in RA reported that age, disease duration, disease activity, pain intensity and hand grip strength were related to physical disability in patients with RA (66). However, only disease activity had an impact on physical function as a small improvement in disease activity results in a large improvement in functional ability. A recent study on gender differences in disease activity in RA has reported that while the disease appears to be worse in women than men, many of the differences may be explained by the measures used to assess disease activity, rather than disease activity itself (67).

Work productivity

Due to the disability associated with both AS and RA, work productivity is severely affected. This is particularly the case for people with AS because the disease strikes at a younger age and affects them as they are entering the workforce and commencing careers, so the socioeconomic impact of the disease on patients and on society is an important issue (2).

Compared with the general population, people with AS have a lower rate of employment, with nearly one-third of younger patients aged <37 years ceasing employment due to the disease. Reported rates of work cessation due to AS range from 13% to 31% (33, 68), and for RA, 19% of cases had ceased work two years after diagnosis. When adjusted for age and gender, the risk for cessation of work in patients with AS aged 16–60 was 3.1 times higher than in the general population (69). Determinants of withdrawal from work were older age at diagnosis, manual work, and coping strategies characterised by limiting or adapting activities.

By 10 years after a diagnosis of RA, 44% had retired as a result of their disease, in part as RA has an older age of onset than AS. Data on the incidence of RA-related work disability in the US has reported that the annual incidence of any work cessation was approximately 10% and arthritis-attributed work cessation was 6% (70). A significant proportion (39%) of cases in this study, who had reported more than one episode of cessation of work, later returned to work.

A review of work loss in RA has reported a median of 66% (range 36-84%) of employed RA subjects experienced work loss due to RA in the previous 12 months, for a median duration of 39 days (range 7-84 days) (71). AS-related sick leave amongst those employed has been reported to be between 6 and 46 days per year (72-74). Age, education, and physical function have been shown to be associated with work disability in AS while peripheral joint disease was associated with sick leave (74).

Gender differences are seen in work disability between AS and RA. Compared to the general population, employment rates for AS patients were significantly decreased in male patients, but not in female patients (72). Both genders, however, experienced increased AS-related (partial) work disability. A comparison of RA-related work disability amongst males and females has found that females with RA had a four-fold increase in work disability compared to males with RA (75).

Case fatality (mortality)

When compared to the general population, both AS and RA result in increased mortality of 1.5 fold for both diseases (76, 77).

The common causes of death in RA are similar to those in the general population for cardiovascular disease and cancer; infection, respiratory disease and renal disease are substantially more common as causes of death in RA than in the general population (76). More than 50% of the reported mortality in AS was due to respiratory complications (78). A high fatality rate from severe consequences of spinal fractures in AS has been reported (79) and mortality from cardiovascular disease has been found to be increased in patients with AS (80).

Remission

Due to the advances in treatment for RA, an increasing number of patients are able to achieve remission. With treatment, rates of remission in RA

are higher than those reported in AS. RA remission without treatment with DMARDs (Disease Modifying Anti-Rheumatic Drugs) has been reported to occur in 9.5–14% of cases and treatment with TNF (Tumour Necrosis Factor) inhibitors in combination with other DMARDs may give remission rates of between 31 and 56% (81). Lower rates of partial AS remission have been reported, ranging from 0% to 31% after TNF-α antagonist treatment (82). It has not been determined whether remission remains after cessation of treatment.

Remission in RA is common during pregnancy (1). However in AS, it has been reported that in 80% of patients disease symptoms were unaltered or aggravated during pregnancy (83).

Risk factors

There is a general consensus that RA is a multifactorial disease, resulting from the interaction between genetic and environmental factors, which contribute to its occurrence and expression (45). Several known risk factors for RA exist and these risk factors offer avenues for possible primary or secondary prevention of the disease.

Smoking: Smoking is likely to influence the occurrence of RA as well as the severity of the disease. The relative risk (RR) of RA was significantly elevated among current (RR 1.43) and past smokers (RR 1.47), compared to people who never smoked (84). However, some studies have not shown an increase in smoking in patients with RA.

Obesity: Having a body mass index (BMI, kg/m^2) ≥30 has been found to be associated with an adjusted odds ratio of 3.74 for developing RA (85).

Sex hormones: Higher occurrence of RA in females suggests some influence of the female hormones. The oral contraceptive pill appears to protect against the development of RA and RA is rare during pregnancy and more common in nulliparous women (1).

Diet: Several epidemiological studies suggest a potential protective effect of lifelong consumption of fish, olive oil, and cooked vegetables (45).

The risk factors for AS are less well reported; however, infectious agents have been regarded as a likely cause of primary AS. *Klebsiella pneumoniae* may be the main microbial agent, being implicated as a triggering and/or perpetuating factor in the aetiopathogenesis of AS (48, 86). The human immunodeficiency virus (HIV) epidemic in black Africans has been associated with the increased prevalence of spondyloarthropathies (87).

Conclusion

The majority of studies of the epidemiology of RA and AS have been conducted in northern Europe and North America. The incidence and prevalence of the diseases are similar, and significant geographic variations are seen in both diseases. There is an increasing trend in the prevalence of AS, whereas RA is reported to be declining. Both diseases result in considerable disability, reduced work productivity and increased mortality.

Many similarities and differences between the characteristics of AS and RA may lead to important clues as to the aetiology of both diseases.

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