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Rheumatoïd arthritis

The natural history of rheumatoid arthritis over 20 years. Clinical symptoms, radiological signs, treatment, mortality and prognostic significance of early features

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SUMMARY *A 20 year follow up is reported on 100 patients with definite or classical rheumatoid arthritis when they were all initially seen within one year of the onset of arthritis. Forty-six patients have died and in 17 death was due to or related to RA. Mortality was greater in men than in women and in patients who had classical rather than definite RA at one year. Thirty of the surviving 54 patients have either no or only moderate restriction of physical activity. Those who had definite RA at one year are now better as regards functional capacity and joint score than those who had classical RA. In general the titre of the Rose test has tended to fall and those who have become seronegative have done better than those remaining seropositive.*

Key words: Natural History, Prognostic Features, Rheumatoid Artritis.

INTRODUCTION

Giving a prognosis for the individual patient with rheumatoid arthritis (RA) is an uncertain exercise. In advising the patient with early RA none of us can foresee with any confidence what his or her condition is likely to be in the years to come. However, a number of reports are now available which help us to make some prediction of the future course of the disease (1-9).

In this review we shall consider the lessons learned from a 20 year prospective study of 100 patients with RA. First we shall discuss the causes of death in the 20 year period, then review the psysical findings in the survivors, the patterns of the course of the arthritis and the prognostic significance of certain early features. Finally we shall describe the radiological changes in the hands and cervical spine and their relationship with corticosteroid treatment.

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The patients

The 100 patients were all seen initially by one of us (JAC) at the Royal National Hospital for Rheumatic Diseases, Bath within a year of the onset of arthritis. All fulfilled the criteria for definite or classical RA. They were treated and followed up at the hospital, with formal reviews at 11, 15, 18 and 20 years. There were 36 men and 64 women of ages ranging from 18 to 81 years (mean 50.6) and the average duration of RA, when they were first seen, was under 4 months.

The causes of death

After 20 years 46 of the 100 patients have died and the causes and circumstances of death are known in all. The deaths were classified into 3 groups: deaths directly due to RA and its systemic complications, deaths due to other causes but with RA or its treatments as a contributory factor and deaths from causes unrelated to RA.

Attributable deaths (n = 9) were mainly due to vasculitis and cardiac complications and to renal failure due to amyloid. Six of these nine patients died between 6 and 11 years after the beginning of the disease, only one during the first six years (after 3 years) and two in the last nine years (at 13 and 16 years).

In 8 cases RA or *its treatment*, especially corticosteroids, *contributed* to death; in 7 of these infections played a role. Apart from 2 cases (1 and 7 years) all these patients died after at least 12 years of disease!

In the *unrelated group* (n = 29) there were no deaths due to infection, but here cardiovascular causes predominated and played a role in most cases: in 11 cases death was due to myocardial infarction. There was a higher overall mortality in men (20 out of 36 = 55.5%) than in women (26 out of 64 = 40.6%), but those men who survive, have less severe disease than the women. There was no correlation between the causes of death and the Rose titre, the existence of nodules, ESR, Haemoglobin, number of joints affected, weight or age, but a correlation was found with functional capacity and ARA grading. We found that the functional capacity after one year of onset was significantly worse in those patients, who died of RA or of its treatment than in the unrelated ($p < 0.01$) and also than that of the survivors ($p < 0.001$) (Fig. 1).

Patients classified as having classical disease at 1 year had significantly increased mortality when compared to those having definite RA ($p < 0.05$). Since classical and definite RA are by definition distinguished only by the number of disease characteristics, it appears that higher mortality is associated with a more complete expression of the disease at one year of onset.

There was a loss life expectancy in all groups: this was most marked in the "attributable" group, whom we estimated to be dying some 15 years prematurely, while in the "contributory" group death was some 10 years premature, and in the unrelated group about 5 years. On this basis we suggest that the generally agreed reduction of lifespan in RA patients in mainly due to a minority of patients who have relatively severe disease and die 10 or more years prematurely as a result. The majority of patients with less severe disease have a nearly normal lifespan and die ultimately of unrelated diseases. The same was found in other studies (10).

In our series lymphoproliferative malignancy (Hodgkin/non Hodgkin lymphoma) was only seen in 1 patient, who happened to be treated with azathioprin, although for a short period, 10 months. Other studies found that the risk of developing malignant lymphomas is independent of treatment with azathioprin and probably also with other immunosuppressive drugs, but rather is generally associated with the severity of rheumatoid arthritis (10).

The survivors

All 54 survivors were seen and assessed at the hospital. There were 16 men (mean age 67 years) and 38 women (mean age 63 years).

The functional capacity of these patients is shown in Table I. Over half (30/54) remained fit for all activities or only moderately restricted in grades 1 and 2; however, 21 were markedly restricted and 3 severely restricted in grades 3 and 4. Comparing these figures with the situation at the 15 year review we find no deterioration over the five years period (Fig. 1). A similar observation has been made in another review (11) and an

Table I *Functional capacity and ARA category in the 54 surviving patients, after 20 years*

Functional capacity grade	M	F	M + F	%
1	7	6	13	24
2	4	13	17	31
3	4	17	21	39
4	1	2	3	6
	16	38	54	10
ARA category				
Probable	7	6	13	24
Definite	2	8	10	19
Classical	7	24	31	57
	16	38	54	100

explanation may be that deaths occurring over the five year period were mainly among the more severely affected patients, leaving the better cases as survivors.

Joint score. Unlike the functional capacity, the number of affected joints in the 54 patients increased progressively between the 11 year and the 20 year reviews, women being affected more than men (Fig. 2). The discrepancy between the unchanging functional capacity and the deteriorating joint score may, at least partly, be explained by the fact that in the course of time more than half of the patients underwent orthopaedic surgery. For example eight of the survivors had hip replacements which were bilateral in five.

Prognostic markers. It is important for

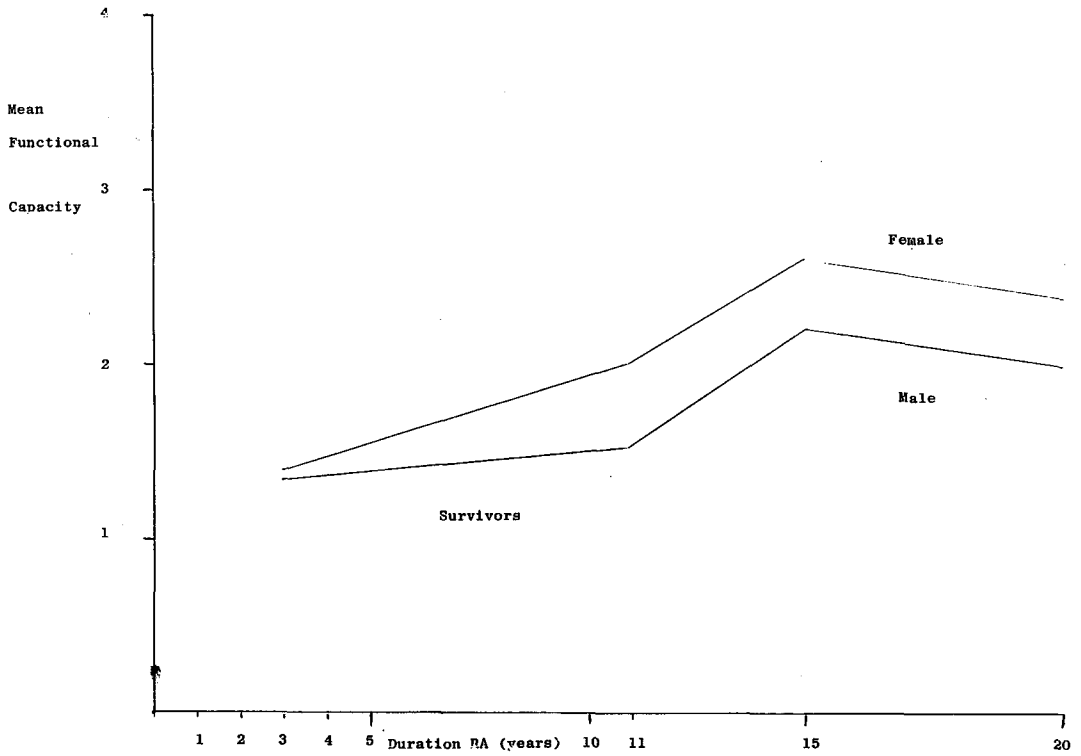

Fig. 1: The "mean" functional capacity during the course of the disease in the 54 survivors, as measured after 3, 11, 15 and 20 years.

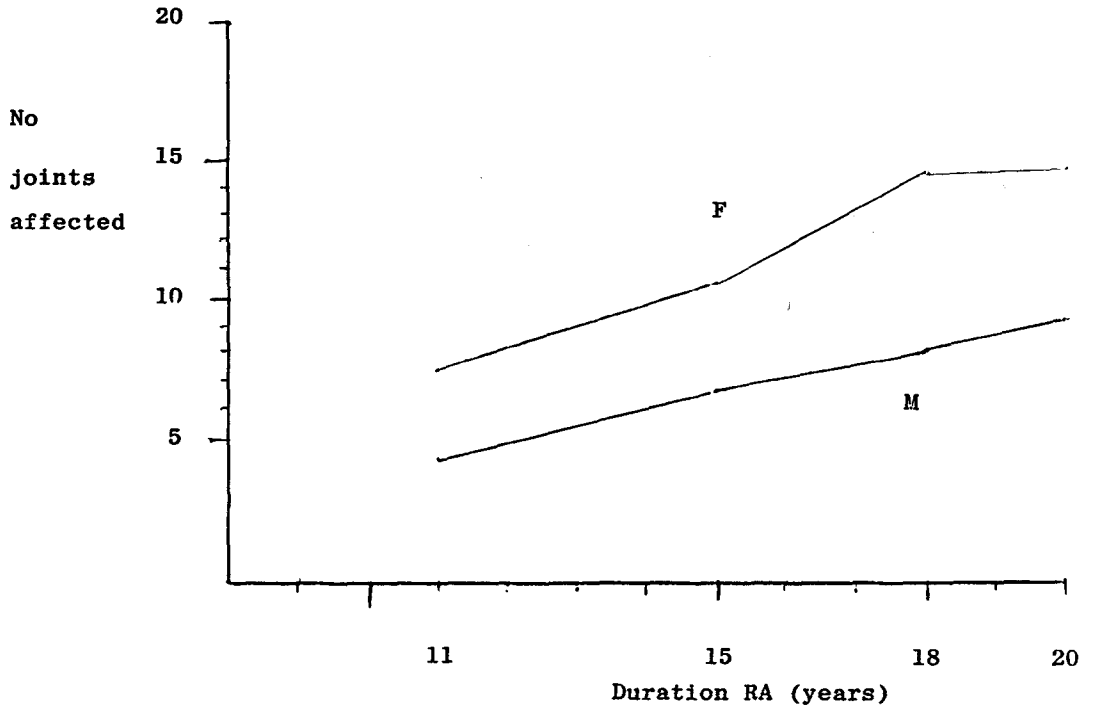

Fig. 2: Number of joints affected in the 54 survivors.

the patient as well as for the rheumatologist to know the prognostic significance of features noted in the early stages of RA - features such as the ESR, haemoglobin, Rose titre, ARA grading and functional capacity.

We have already mentioned that more patients died as a result of RA, who had a worse ARA grading and worse functional capacity after one year of disease (7). What are the findings of ARA criteria and functional capacity in the survivors?

The ARA category at one year appears to be a good prognostic guide. More of those who had definite RA at one year subsequently improved to the category of probable RA (Table IIa). They were better off

Table IIa *ARA category in the survivors at 1 year as prognostic guide*

ARA category at 1 year	ARA category at 20 years			Functional capacity at 20 years	
	prob.	def.	class.	1 + 2	3 + 4
Definite 31 (10 M + 21 F)	12	4	15	21	10
Classical 23 (6 M + 17 F)	1	6	16	9	14
		NS			$p < 0.05$

Table IIb *ARA category in survivors at 1 year as prognostic guide*

ARA category at 1 year		Joint Score at 20 years Mean	(S.D.)	Ritchie index at 20 years Mean	(S.D.)
	10 M	*6.6	(5.7)	2.6	(3.4)
Definite					
n = 31	21 F	**12.3	(7.5)	6.9	(5.5)
	6 M	*13.8	(4.1)	4.3	(4.0)
Classical					
n = 23	17 F	**18.4	(6.2)	10.6	(8.7)
*p<0.01 ; **p<0.02				NS	

Table III *Functional capacity at 20 years in relation to seropositivity*

Functional capacity at 20 years. Both sexes	N	Grades 1 + 2	Grades 3 + 4
Seropositive	25	10	15
Converting to negative	22	16	6
Always negative	7	4	3
	54		
seropos. vs converting p < 0.05			
seropos. vs all neg. p < 0.05			

Table IV *ARA categories at 20 years in relation to seropositivity*

		Probable + definite	Classical
Sero positive	25	5	20
Converting to negative	22	13	9
Always negative	7	5	2
seropos. vs converting p < 0.01			
seropos. vs all neg. p < 0.02			

regarding functional capacity after 20 years and also the number of joints affected after 20 years was less in this group compared with those with classical RA (Table IIb).

We have shown that the Haemoglobin level at 1 year was a valid indicator of their levels after 11 and 15 years ($p < 0.001$). Also the functional capacity after 1 or 3 years was clearly a prognostic sign for its level after 11 and 15 years of disease ($p < 0.001$).

However the ESR at one year did not prove to be a reliable guide; it did not correlate with its values at 11 years and only weakly so with its value at 15 years.

The Rose Waaler titre appears to be an important clinical marker. Its titre after 1 year correlated significantly with the titres after 11 and 15 years ($p < 0.001$) and also with the number of ARA criteria present ($p < 0.001$) and with the number of joints affected ($p < 0.05$). But the clinical importance of the Rose test is limited as it did not correlate with the functional capacity after 11 or 15 years. After 11 years the Rose test correlated weakly with X-ray abnormalities in the large joints ($p < 0.05$), but not so in

the small joints. But after 15 years there was a correlation of the Rose titre with the severity in mcp and carpal joints (14).

The Rose titre changes frequently in the course of time. Seven of the 54 survivors remained seronegative throughout and 22 have converted from positive to negative (Rose < 1:32). The titre of the others has fallen from an original mean of 1:1024 to 1:128. Those patients who are seronegative after 20 years (9 men and 20 women) are now better off than the rest regarding functional capacity, and also regarding ARA category, joint score, Ritchie index and plasma viscosity, showing the clinical significance of a positive or negative Rose Waaler test. As the patients who converted to seronegative behave very much like those persistently seronegative, our findings do not support the idea of seropositive and seronegative RA being separate entities as is sometimes suggested.

Does the disease change in the course of time?

The long term pattern of disease over the 20 years was one of chronic persistent activity in 25, a remitting and relapsing course in 12, a sustained remission in 12 and an atypical course in 5 (Table V).

As one may expect those with chronic persistent disease were more frequently seropositive and had clearly worse functional capacity. The findings may give stronger support to the idea that second line drugs must be given especially to those patients with chronic persistent RA.

The HLA DR4 antigen is frequently said to correlate with severity of RA. So this was tested in 52 of the survivors; DR4 was present in 82.4% (controls 27%) and Dw4 in 60.4% (controls 25.2%). To our surprise in our series no correlation could be found between the presence of DR4 and seropositivity, functional capacity, disease pattern or sex.

Our series was incorporated into a larger study by Jaraquemeda et al (12). In this larger series correlations were found between the presence of DR4 antigen and seropositivity. Among other interesting observations subluxation of cervical spine was associated with HLA B27 (this antigen was found in 25% of the cases with subluxation, compared with 8.2% in those without subluxations).

Did the use of corticosteroids influence the course of the disease?

All of the patients who died due to RA or its treatment had been treated with corticosteroids (7). This may be explained by the fact that they had more serious disease and stronger indications for the use of corticosteroids. Is there an influence of corticosteroid treatment on X-rays of cervical spine, hands and feet? In the cervical spine

Table V *Pattern of disease over 20 years and functional grading*

	Patients				Functional capacity grade	
Pattern	No.	M	F	sero positive	1 + 2	3 + 4
Remitting	12	5	7	2	9	3
Chronic relapsing	12	3	9	5	8	4
Chronic persistent	25	4	21	17	9	16
Atypical	5	4	1	1	4	1
Total	54	16	38	25	30	24

erosions and narrowed disc spaces may be seen. These abnormalities correlated with all indicators of severity of RA such as ESR, Rose titre, Hb, Functional capacity, presence of nodules, ARA-grading (14). Subluxation alone, whether assessed in the cervical spine as a whole or in the atlanto- axial joint alone, was less closely related to disease activity and on average greater in patients treated with corticosteroids. It tended to increase in relation to duration of treatment. This finding was later confirmed in other studies including one in patients with chronic asthmatic bronchitis treated with corticosteroids (13) at least in the lower segments.

Radiological signs of damage in the mcp-joints and carpal bones correlated with both the degree of damage and the degree of subluxation in the cervical spine as well as with corticosteroid treatment (14). Mutilans deformities at the mcp-joints (with telescoping of the fingers) were also found exclusively in patients treated for more than 2 years with corticosteroids. It was also highly significantly associated with subluxation in the neck (14).

The future well being of an RA patient will always be difficult to predict. But we now know that certain early features will enable us as clinicians to tell the patient, cautiously, something about his future. For example a very good functional capacity after one to three years is a good prognostic sign and we may reassure him that he will probably have a good functional capacity still after 15 or 20 years. The same holds true for a negative Rose Waaler test.

We would like to stress the importance of continuing studies regarding the natural history in patients with rheumatoid arthritis.

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