

Significance of positive tests for rheumatoid factor in the prognosis of rheumatoid arthritis

A follow-up study

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Ragan (1949) found that, in a large group of patients with rheumatoid arthritis (RA) after a mean follow-up period of 11 years, those with a negative serological agglutination test for group-A haemolytic streptococci (a method for detecting rheumatoid factor) had a far better prognosis with regard to the joint abnormalities than those with a positive test.

In the past 15 years other observers, using a variety of other tests for rheumatoid factor, confirmed the difference in prognosis between sero-positive and sero-negative cases with regard to a number of criteria. A higher percentage of remissions was observed in sero-negative RA (Kellgren, 1957; Otten and Westendorp Boerma, 1959), a more extensive deterioration in the x-ray abnormalities in sero-positive RA (Kellgren, 1957; Ragan and Farrington, 1962; Hill and Greenbury, 1965; Sievers, 1965) and a greater improvement in functional capacity, disease activity, haemoglobin (Hb), and erythrocyte sedimentation rate (ESR) in sero-negative RA (Duthie, Brown, Knox, and Thompson, 1957; Duthie, Brown, Truelove, Baragar, and Lawrie, 1961).

All investigators considered a positive serology a poor prognostic sign in RA, but in none of the published reports were sero-negative patients matched with a control group of sero-positive cases. Moreover, only a few criteria were analysed in comparing the two groups. It therefore seemed desirable to re-examine the prognostic significance of sero-positivity by means of a follow-up study of a matched group of sero-negative and sero-positive patients, analysing seven features, each of which could be regarded as an expression of the activity of the rheumatoid process.

Material and methods

During the 5-year period 1958 to 1962 inclusive, 192 patients with sero-negative polyarthritis were seen in our department; some of them had been known to us before 1958. The group does not include cases of polyarthritis

associated with psoriasis, colitis, ankylosing spondylitis, or a positive LE-cell phenomenon, patients with a diagnosis mentioned in the list of exclusions of the ARA criteria for RA (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959), and those in whom the onset of joint symptoms began before the age of 15 years.

Nearly all patients fulfilled the ARA criteria for definite and/or classical RA at some point in the course of their disease. Only a few had to be classified as probable cases of RA.

In a number of patients the diagnostic criteria for definite RA were not fulfilled at the time of the first visit. By 1966, eighteen of these 192 patients had died and 39 had developed a positive serology (22 per cent. of the remaining 174). Of the remaining 135 sero-negative patients, 130 have been re-examined: a completion rate of 96 per cent. This sero-negative group has been matched with a sero-positive control group with regard to sex, age, and duration of illness (Tables I, II, and III). For the sero-positive patients the same criteria for exclusion were applied as for the sero-negative cases. In both groups the mean age of the men was 5 years older than that of the women. In both groups the mean duration of illness was 3 years longer in the women than in the men. There was no significant difference between the mean duration of follow-up. From these data two conclusions can be drawn:

(1) Sero-positive and sero-negative males and females have to be compared separately.

Table I *Clinical details in 1967 of the two groups of patients studied*

Serology	Positive		Negative	
	Male	Female	Male	Female
No. of patients	35	95	35	95
Mean age (yrs)	60.1	55.2	61.0	55.4
Mean duration of illness (yrs)	11.6	14.5	11.3	14.2
Mean observation period (yrs)	7.0	8.2	6.5	7.8

Table II Sero-positive and sero-negative polyarthritis, by age and sex, 1967

Age group (yrs)	Sex			
	Male		Female	
	Sero-positive	Sero-negative	Sero-positive	Sero-negative
≤34	1	2	5	6
35-44	4	3	16	16
45-54	4	5	20	22
55-64	12	11	29	23
65-74	8	7	21	21
>75	6	7	4	7
Total	35	35	95	95
Mean	60.1	61.0	55.2	55.4

Table III Sero-positive and sero-negative polyarthritis, by sex and duration of illness, 1967

Duration of illness (yrs)	Sex			
	Male		Female	
	Sero-positive	Sero-negative	Sero-positive	Sero-negative
5-9	23	22	37	39
10-14	4	4	26	23
15-19	3	5	11	9
20-24	3	2	8	9
≥25	2	2	13	15
Total	35	35	95	95
Mean	11.6	11.3	14.5	14.2

(2) In our sample the onset of sero-negative RA occurred later in the males than in the females.

At the first and second assessments the following features were evaluated:

(1) Number of ARA criteria fulfilled (excluding serology).

(2) ESR (Westergren).

(3) Hb.

(4) Functional capacity (Steinbrocker, Traeger, and Batterman, 1949).

(5) X-ray abnormalities of the joints (Steinbrocker, Traeger, and Batterman 1949). For each patient a mean stage was calculated for the small joints (metacarpophalangeal, proximal interphalangeal, and metatarsophalangeal) and the large joints (shoulders, elbows, wrists, hips, knees, and ankles). All patients had radiographs of the hands and feet and of other joints that were swollen and/or showed limitation of movement. The joints which seemed to be normal by physical examination and were not x rayed were graded as Stage I.

At the second examination the sacroiliac joints of all

patients were x rayed. A diagnosis of sacroiliitis was made on the strength of irregularities of the joint surface (with or without periarticular sclerosis) or of fusion of the joint.

(6) Subcutaneous rheumatoid nodules.

(7) Number of joints involved. A joint was considered as being involved in the rheumatoid process if it was swollen or deformed or showed limitation of movement. The metacarpophalangeal joints of one hand were considered as one joint. The same procedure was applied for the proximal interphalangeal, distal interphalangeal, and metatarsophalangeal joints. In this way a total of twenty joints or groups of joints was analysed in each patient: both shoulders, elbows, wrists, hips, knees, and ankles, metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints of each hand, and the metatarsophalangeal joints of each foot.

The examination carried out at the first visit to our department was regarded as the first assessment whether a definite diagnosis could be made or not.

At the second examination, carried out in 1966 and 1967, two tests for rheumatoid factor were performed, one using human erythrocytes (Valkenburg, 1963a) and the other latex particles (Valkenburg, 1963b). If the first examination had been made before 1957, only a sheep-cell or a human erythrocyte agglutination test had been done but in almost all patients the latex-fixation test was performed some years later and we regarded the result of the first latex-fixation test in each patient as pertaining to the first examination. In the sheep-cell or the human red cell agglutination test a titre of 1 in 32 or over was considered as positive, in the latex-fixation test a titre of 1 in 640 or over.

For the statistical analysis of the results of this study the χ^2 test was used, applying Yates' correction when necessary.

Results (see Table V, overleaf)

Table V (summarized in Table IV) shows that, at the time of the first assessment, in the sero-positive group

Table IV Serology related to symptoms and signs, by sex

Assessment	First		Second	
	Male	Female	Male	Female
Sex	+	-	+	-
Serology	+	-	+	-
ARA criteria	n.s.	n.s.	+	+
Erythrocyte sedimentation rate	n.s.	n.s.	+	+
Haemoglobin	n.s.	n.s.	n.s.	+
Functional capacity	n.s.	n.s.	+	+
Radiological abnormalities	n.s.	n.s.	+	+
Severity Large joints	n.s.	n.s.	+	+
Small joints	+	n.s.	+	+
Nodules	+	+	+	+
No. of joints involved	n.s.	n.s.	n.s.	+

+ significant at ≤5 per cent. level
n.s. not significant.

Table V *Clinical signs and symptoms in follow-up study*

<i>Sex</i>		<i>Male</i>				<i>Female</i>			
		<i>First</i>		<i>Second</i>		<i>First</i>		<i>Second</i>	
<i>Assessment</i>		<i>Positive</i>	<i>Negative</i>	<i>Positive</i>	<i>Negative</i>	<i>Positive</i>	<i>Negative</i>	<i>Positive</i>	<i>Negative</i>
<i>Serology</i>									
No. of ARA criteria (serology not included)	>5	25	22	25	9	64	57	71	44
	3-4	5	9	8	8	20	28	16	16
	0-2	5	4	2	18	11	10	8	35
	Total	35	35	35	35	95	95	95	95
	χ^2	1.4456		20.3296		1.7856		23.2928	
	P	>0.30		<0.0005		>0.10		<0.0005	
Subcutaneous rheumatoid nodules	Present	9	2	13	0	14	3	26	7
	Absent	26	33	22	35	81	92	69	88
	Total	35	35	35	35	95	95	95	95
	χ^2	3.8826		13.6008		6.4600		11.8746	
	P	<0.05		<0.0005		<0.02		<0.001	
Radiological abnormalities	Present	25	21	35	29	63	52	93	71
	Absent	10	13	0	6	31	43	2	24
	Total	35	34	35	35	94	95	95	95
	χ^2	0.5877		4.70		2.6831		19.6466	
	P	>0.30		<0.05		>0.10		<0.0005	
Functional capacity	Class I	6	4	7	18	9	12	16	36
	Class II	23	23	20	12	67	64	49	43
	Class III-IV	5	7	8	5	19	19	30	16
	Total	34	34	35	35	95	95	95	95
	χ^2	n.d.*		7.5324		n.d.*		12.3444	
	P			<0.025				<0.005	
Erythrocyte sedimentation rate (mm./1hr: Westergren)	0-9	4	10	6	16	10	15	16	30
	10-19	8	5	11	10	20	22	24	29
	20-39	7	7	9	7	30	34	33	23
	>40	16	13	9	2	35	24	22	11
	Total	35	35	35	35	95	95	95	93
χ^2	3.5744		9.2976		3.3960		10.1649		
	P	>0.30		<0.05		>0.30		<0.02	
Haemoglobin (per cent.)	>80	20	17	32	32	18	27	63	80
	70-79	11	10	2	3	51	46	26	11
	50-69	4	5	1	0	26	22	6	3
	Total	35	32	35	35	95	95	95	94
χ^2	n.d.*		n.d.*		2.3908		9.0970		
	P					>0.30		<0.02	
Radiological aspect (mean Small stage) joints	1.00-1.09	15	24	4	19	54	66	14	49
	1.10-1.59	15	10	15	14	22	23	38	29
	1.60-2.09	2	0	8	2	10	3	18	11
	>2.10	3	0	8	0	8	3	25	6
	Total	35	34	35	35	94	95	95	95
χ^2	4.7770		12.7008		7.2594		33.9880		
	P	<0.05		<0.001		>0.05		<0.0005	

continued

Table V continued

Sex		Male				Female			
Assessment		First		Second		First		Second	
Serology		Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
Large joints	1·00-1·09	22	26	9	19	64	64	28	53
	1·10-1·59	10	5	14	13	20	23	32	26
	>1·60	3	3	12	3	10	8	35	16
Total		35	34	35	35	94	95	95	95
χ^2		2·0260		9·0088		n.d.*		15·4152	
P		>0·30		<0·02				<0·0005	
No. of joints involved	0-2	4	3	4	8	19	20	8	34
	3-5	9	11	5	7	25	27	15	13
	6-8	10	12	6	11	18	22	16	16
	9-11	4	4	6	7	18	16	19	15
	12-14	5	3	5	0	6	7	20	1
	15-20	3	2	9	2	9	3	17	16
Total		35	35	35	35	95	95	95	95
χ^2		n.d.*		8·4800		3·6968		33·9292	
P				>0·05		>0·50		<0·0005	

there were significantly more patients with nodules and that the severity of the radiological destructive changes in the small joints was significantly greater in the males.

The two groups did not differ originally with regard to the number of ARA criteria, ESR, Hb, functional capacity, prevalence of radiological abnormalities, severity of radiological abnormalities of the large joints, or the number of joints involved.

At the time of the second assessment there was also a statistically significant difference for both males and females in number of ARA criteria (more in the sero-positive groups), ESR (higher in the sero-positives), functional capacity (worse in the sero-positives), prevalence of radiological abnormalities (more in the sero-positives), and severity of radiological abnormalities of both the small and large joints (greater in the sero-positives). For females only there were significantly more sero-positive patients with lower Hb values and a greater number of joints involved.

Table VI summarizes significant changes for better or worse between the first and second assessments:

(1) In the sero-negative groups, male and female, the number of ARA criteria decreased ($P < 0\cdot001$ and $< 0\cdot0005$ respectively).

(2) There was an improvement in the functional capacity in the sero-negatives (P for the males $< 0\cdot005$; for the females $< 0\cdot0005$).

(3) There was a decrease in the ESR of the sero-negatives (P for the males $< 0\cdot02$; for the females $< 0\cdot005$).

Table VI Significant changes between first and second assessments

Change	Better	Worse
Group		
Sero-negative	ARA criteria Functional capacity Erythrocyte sedimentation rate Haemoglobin	Radiology (Females only)
Sero-positive	Haemoglobin	Number of joints involved Radiology

(4) Hb rose in all groups (P for both female groups $< 0\cdot0005$; P for both male groups $< 0\cdot005$).

(5) The sero-positive male and female patients showed an increase in the total number of joints involved (for each group $P < 0\cdot0005$). For the sero-negative males and females 54 and 56 per cent. respectively of joints were not involved at either assessment, 19 and 20 per cent. were involved at both assessments, and 16 and 11 per cent. showed recovery but were replaced by a similar number of other joints that had developed signs of arthritis in the interval, so that there was no appreciable change in the total number.

(6) The sero-positive males and females showed an

increase in the number of patients with radiological abnormalities (males: $P < 0.005$; females: $P < 0.0005$), as well as in their severity in both the large joints (males: $P < 0.005$; females: $P < 0.0005$) and the small joints (males: $P < 0.01$; females: $P < 0.0005$). The sero-negative females also showed an increase in the number of patients with radiological abnormalities ($P < 0.01$), and in their severity in the small joints only ($P < 0.05$).

Discussion

None of the sero-negative patients developed psoriasis or any of the diseases mentioned in the list of exclusions of the ARA criteria. At the end of the observation period four male and two female sero-negative patients and one male and one female sero-positive patient showed the radiological appearance of unilateral or bilateral sacroiliitis; there were no other abnormalities of the spine in these patients indicative of ankylosing spondylitis. At the end of the observation period erosions of the distal interphalangeal joints of the fingers, usually regarded as typical for psoriatic arthritis (Reed and Wright, 1966), were somewhat more frequent in the sero-negative cases. Osteoarthritis of the distal interphalangeal joints occurred in both groups in about the same frequency. Two patients, one female sero-positive and one female sero-negative, developed a positive LE-cell phenomenon without further clinical manifestations of systemic lupus erythematosus. We could thus find no indications of disease process other than RA to explain the sero-negative polyarthritis.

We cannot explain why sero-negative RA began in males an average of 8 years later than in females. As far as we know, a similar finding has never been reported in the literature. For RA in general (irrespective of serology), Short, Bauer, and Reynolds (1957a), Duthie, Thompson, Weir and Fletcher (1955), and Sievers (1965) did not find indications of a later onset in males than in females.

From this follow-up study we may conclude that the prognosis in sero-negative RA is better than that in sero-positive RA. Some features which may be influenced by the activity of the rheumatoid process—total number of ARA criteria, functional capacity, and ESR—improved only in the sero-negative groups during the follow-up period.

Sievers (1965) also found improvement of the inflammatory activity in sero-negative but not in sero-positive patients in a follow-up study.

The Hb value is also generally regarded as an indicator of the activity of the rheumatoid process, but it is less accurate and less sensitive than the erythrocyte sedimentation rate. In all four groups the Hb rose, but at the second assessment it was significantly higher in the sero-negative than in the sero-positive females. Short, Bauer, and Reynolds

(1957b) also noticed that in patients with RA the frequency of anaemia decreased after a longer duration of illness.

In spite of a decline in the activity of the rheumatoid process in the sero-negative patients, the total number of clinically involved joints did not decrease. This indicates that in some sero-negative patients with RA the arthritis persists although the symptoms of activity may be few. It could also be that a long-standing inflammation tends to cause permanent anatomical damage to the joints. Sievers (1965) recorded a decrease in the number of clinically affected joints in his sero-negative patients (and even in his weakly sero-positive patients), but he took tenderness on passive motion or on direct pressure as an indication of joint involvement. As we only used swelling and/or limitation of movement as signs of involvement, our results and those of Sievers cannot be compared.

The prognosis of thirteen women and one man, originally sero-positive, who later became sero-negative did not differ from the prognosis of the consistently sero-positive patients. The prognosis of 32 women and seven men, originally sero-negative, who later became sero-positive lay between that of the sero-positives and the sero-negatives.

Sero-negativity does not mean absence of rheumatoid factor. Klein, Valkenburg, van Zwet, and Lafeber (1966) demonstrated that the presence of rheumatoid factor can be obscured by an inhibitor belonging to the complement system. Inactivation of the inhibitor is needed before the true titre of the rheumatoid factor can be estimated. Our study indicates that the presence of uninhibited rheumatoid factor in a patient with RA is related to a less favourable prognosis. This does not mean that rheumatoid factor has a pathogenetic influence in RA; it may be only another by-product of an unknown primary process. This study reaffirms the view of Kellgren (1957) that in studies of the prognosis and treatment of RA the sero-positive and sero-negative groups must be evaluated separately.

Summary

(1) 130 patients with polyarthritis sero-negative for rheumatoid factor have been compared with a matched control group of patients with rheumatoid arthritis sero-positive for rheumatoid factor.

(2) Rheumatoid nodules were more prevalent in the sero-positive group, and in the sero-positive males the severity of the x-ray changes in the small joints was greater. After 7 to 8 years, the sero-positive group was in a worse condition than the sero-negatives with regard to the number of ARA criteria, erythrocyte sedimentation rate, Hb per cent., functional capacity, erosions of large and small joints, presence of nodules, and number of involved joints.

(3) During the follow-up period the following changes were observed:

Sero-negative (male and female): Improvements in number of ARA criteria, functional capacity, erythrocyte sedimentation rate, and Hb per cent.

Sero-negative (female): Increase in severity of erosions of small joints.

Sero-positive (male and female): Improvement in Hb per cent., deterioration with regard to the total number of involved joints and severity of x-ray

abnormalities in large and small joints.

(4) In this sample the onset of the sero-negative polyarthritis occurred in males on average of 8 years later than in females.

(5) In view of the difference in prognosis between sero-positive and sero-negative polyarthritis, the results of follow-up studies or clinical trials must be evaluated separately for sero-negative and sero-positive patients.

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RÉSUMÉ

La signification des tests positifs pour le facteur rhumatoïde dans le pronostic de l'arthrite rhumatoïde.

(1) 130 malades atteints de polyarthrite séro-négative au facteur rhumatoïde ont été comparés à un groupe de témoins similaire de malades séro-positifs.

(2) Des nodules rhumatoïdes étaient plus souvent vus dans le groupe séro-positif, et chez les hommes séro-positifs la gravité des changements radiologiques des petites articulations était plus marquée. 7 à 8 années plus tard le groupe séro-positif était dans un plus mauvais état que le groupe séro-négatif quant au nombre de

SUMARIO

Significado de las pruebas positivas en busca de factor reumatoïde en la prognosis de la artritis reumatoïde

(1) 130 pacientes con poliartrosis seronegativa de factor reumatoïde han sido comparados con un grupo testigo similar de pacientes con artritis reumatoïde seropositiva.

(2) Los nódulos reumatoïdes eran más frecuentes en el grupo seropositivo, y en los hombres seropositivos era mayor la severidad de las alteraciones radiológicas en las articulaciones pequeñas. Siete a ocho años más tarde, los seropositivos se hallaban en peor condición que los seronegativos con respecto al número de la pauta

critères A.R.A., à la vitesse de sédimentation, au pourcentage d'hémoglobine, à la compétence fonctionnelle, aux érosions des petites et des grandes articulations, à la présence des nodules, et au nombre des articulations affectées.

(3) Pendant la période de surveillance les changements suivants ont été observés:

Hommes et femmes séro-négatifs: Des améliorations au nombre des critères A.R.A., à la compétence fonctionnelle, à la vitesse de sédimentation, au pourcentage d'hémoglobine.

Femmes séro-négatives: Une augmentation dans la gravité des érosions des petites articulations.

Hommes et femmes séro-positifs: Une amélioration du pourcentage, une augmentation du nombre total des articulations affectées et de la gravité des anomalies radiologiques des grandes et des petites articulations.

(4) Dans cette étude le début de la polyarthrite séro-négative avait lieu chez les hommes, en moyenne 8 années plus tard que chez les femmes.

(5) En raison de la différence entre le pronostic de la polyarthrite séro-positive et séro-négative, les résultats des enquêtes ou des essais cliniques devraient être évalués séparément pour les malades séro-négatifs et ceux séro-positifs.

A.R.A., el ESR, Hb por ciento, capacidad funcional, erosión de articulaciones grandes y pequeñas, presencia de nódulos y número de articulaciones afectadas.

(3) Durante el período complementario se observaron los siguientes cambios:

Seronegativo (hombres y mujeres): Mejoras en el número de la pauta A.R.A., en la capacidad funcional, velocidad de sedimentación de eritrocitos and Hb por ciento.

Seronegativo (mujeres): Aumento en la severidad de erosiones de articulaciones pequeñas.

Seropositivo (hombres y mujeres): Mejora en el Hb por ciento, deterioro con respecto al número total de articulaciones afectadas y severidad de las anomalías radiológicas en articulaciones grandes y pequeñas.

(4) En este grupo la poliartritis seronegativa principió en los hombres un promedio de ocho años más tarde que en las mujeres.

(5) En vista de la diferencia en la prognosis entre poliartritis seropositiva y seronegativa, los resultados de estudios o pruebas clínicas deben ser evaluados separadamente para pacientes seronegativos y seropositivos.