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Clinical arthritis associated with positive radiological and serological findings in Finnish adults

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Summary. The Mini-Finland Health Survey was designed to analyse the epidemiology of major public health problems. The study covered a representative sample of the Finnish population aged 30 years or over, and initially comprised 8 000 people. Serum rheumatoid factor was determined in 7 124 cases (89%). There were 138 cases of clinical arthritis in the series, corresponding to a prevalence of 1.9% (1.0% in males and 2.7% in females). Fifty-nine of the cases (0.8% of the population) were seropositive, and 50 cases (0.7%) had in their hand radiographs changes characteristic of rheumatoid arthritis. Twelve of the X-ray positive cases were seronegative. One-half of these proved to be seroconversion cases or rheumatoid variants typically seronegative, such as early-onset juvenile rheumatoid arthritis.

Key words: Rheumatoid arthritis – Rheumatoid factors – Epidemiology

Introduction

Epidemiological studies of rheumatoid arthritis (RA) aimed at finding etiological clues to the disease on the basis of its occurrence in representative population samples were started in England in the 1950s, and they soon expanded into comparative international surveys [1, 2]. The information accumulated by the end of the 1960s suggested a rather uniform prevalence of definite RA approaching 1% in most Caucasian groups [3]. Variation from this figure may have been due to methodological issues, although the existence of real differences could not be excluded [4]. Subsequently, higher figures have been reported for certain North American Indian tribes [3, 5], whereas the prevalence of RA may be quite low among some rural African black populations [6].

Further descriptive studies on the prevalence of RA are not expected to provide clues to the etiology and pathogenesis of the disease [5]. The Mini-Finland Health Survey is a multidisciplinary study with musculoskeletal diseases as one of its main targets. The study also includes a follow-up. In the present communication we report the prevalence data on RA with special reference to rheumatoid factor (RF)-positivity and radiological changes. Incidence events in relation to these cross-sectional data will be the subject of a separate report.

Subjects and methods

Study sample. The Mini-Finland Health Survey was designed to analyse the epidemiology of major public health problems, the need for and adequacy of care, and disability and handicap among the adult population [7]. The study sample was a two-stage cluster sample [8] selected to be representative of the Finnish population aged 30 years or over. The randomization was performed with respect to geographical area, population density, and the proportion of industrial and agricultural workers in the population. The sample consisted of 8 000 people from 40 areas.

Screening. The examinations were carried out in 1978–1980 by the Mobile Clinic of the Social Insurance Institution in two main phases, a screening phase and a reexamination phase. A total of 7 217 subjects (90% of the sample) participated in the screening phase. The subjects received a basic questionnaire inquiring, among other things, about previous diseases and the use of medical services. A separate interview dealt specifically with symptoms of the musculoskeletal system. To detect functional limitations of joints, an examination comprising ten test movements was carried out.

Reexamination. The subjects with a disease history, symptoms, or findings suggesting musculoskeletal disease (3 775 people) were asked to come for reexamination which was performed 3 to 4 months later; 3 437 (90%) subjects participated. The reexamination comprised a standardized physical examination car-

ried out by seven specially trained physicians. It included measures for grading deformity, mobility, and tenderness of all limb joints. Peripheral arthritis was graded on the basis of medical history, symptoms, and physical examination as "definite" or "probable" (these terms do not refer to the American Rheumatism Association's classification criteria) and further divided into different diagnostic categories. The present study deals with patients having clinical arthritis not fulfilling the criteria for other forms of specific arthritis such as psoriatic arthropathy or ankylosing spondylitis with peripheral joint involvement. These patients were operationally defined as having RA. At the examination they all had evidence of active inflammation or the presence of deformities in at least two limb joints. For the subjects who did not participate in the reexamination, the diagnosis was assessed on the basis of information obtained during the screening phase.

In order to assess the sensitivity of the screening methods, a random subsample of 740 people underwent reexamination irrespective of the screening results. Arthritis was diagnosed in 12 of the 383 screening-positive persons but in none of the 357 screening-negative person.

RF testing. As part of the screening phase, blood was taken for serological studies. The Waaler-Rose (sensitized sheep cell agglutination) test was performed for 7 124 people, who form the population of the present study. The following cases were selected for further analysis:

- Subjects with clinical arthritis (cases with diagnosis other than RA not included)
- Subjects with a positive Waaler-Rose test result
- A control matched for age, sex, and place of residence for each of the above cases.

Stored sera from these subjects were retested for RFs in 1986 using Waaler-Rose and latex tests. In the Waaler-Rose test, the geometric mean value of the two determinations was taken as the final result.

The Waaler-Rose test was performed on microtitre plates with U-shaped wells. Natural agglutinins were first absorbed from the serum to be tested. Sheep red blood cells were sensitized with one-third of the minimum agglutinating dose of amboceptor obtained by prolonged immunization. The plates were stored overnight at 4 °C in a refrigerator, after which the readings were made on the basis of sedimentation patterns. Titres ≥ 32 (geometric mean of the two determinations) were regarded as positive.

The latex slide test (Rapi Tex-RF; Behringwerke, Marburg, FRG) was performed on heat-inactivated serum, starting from dilution 1:5 and using equipment devised for the cardiolipin flocculation (VDRL) test for syphilis. According to the manufacturer, a serum dilution of 1:5 corresponds to an RF concentration of about 20 IU/ml.

X-ray examinations. To diagnose osteoarthrosis and RA, posteroanterior X-ray pictures of the hands and wrists were taken for the subjects participating in the reexamination. The diagnosis of osteoarthrosis was based on the criteria presented in the *Atlas of standard radiographs of arthritis* [9], whereas criteria developed by Larsen et al. [10] were used for the assessment of changes characteristic of RA. The readings were all made by one radiologist without any information on the clinical or serological findings. In subjects considered to have peripheral arthritis on the basis of the screening examination, but who did not participate in the reexamination, information on radiographs was requested from hospital and outpatient clinic records. Cases in which erosive changes had been documented at about the same time or prior to the reexamination were regarded as meeting the roentgenological RA criterion. No information on the X-ray status was obtained for one seronegative subject with "definite" arthritis and for seven seronegative subjects with "probable" arthritis.

Table 1. Prevalence of clinical arthritis in the Mini-Finland Health Survey

	Number of cases		
	Males	Females	Total
"Definite" arthritis	18	64	82
"Probable" arthritis	15	41	56
Total with arthritis	33	105	138
Total examined	3 268	3 856	7 124
Prevalence	1.0%	2.7%	1.9%

Table 2. Occurrence of clinical arthritis in relation to the Waaler-Rose titre

Waaler-Rose titre	Cases with clinical arthritis/ total number of cases	
$\geq 2\,000$	5/7	71%
500 – 1 000	13/33	39%
128 – 250	12/56	21%
32 – 64	10/73	14%
Total positives	40/169	24%
<32	98/6 955	1.4%

Results

On clinical grounds, 82 subjects in the study series were considered to have a "definite" and 56 subjects a "probable" RA (Table 1). This corresponds to an overall prevalence of 1.9%.

Symmetrical joint affection, either deformities or soft tissue swelling, was observed in 82% of cases with "definite" and in 67% of cases with "probable" arthritis. Active inflammation in at least three different joint areas as evidenced by soft tissue swelling or hydrops was recorded for 43% of cases with "definite" and for 11% of cases with "probable" arthritis. Ulnar deviation of the fingers and atrophy of the interosseous muscles of the hand each were noted in one-third of cases with "definite" and in about 10% of cases with "probable" arthritis. Rheumatoid nodules were present in 14% of cases with "definite" arthritis.

The prevalence of positive Waaler-Rose test reactions was 2.4%. Positive reactions were associated with clinical arthritis in slightly less than one-quarter of the cases (Table 2). The proportion increased with increasing Waaler-Rose titre; five of the seven cases in the highest titre group ($\geq 2\,000$) had arthritis. Only five of the Waaler-Rose positive arthritis cases had a "probable" disease, in 35 cases

Table 3. Prevalence of seropositive arthritis by age and sex

Age (years)	Prevalence of arthritis		
	Males	Females	Total
30–39	1/887 (0.1%)	2/950 (0.2%)	3/1 837 (0.2%)
40–49	2/827 (0.2%)	6/792 (0.8%)	8/1 619 (0.5%)
50–59	4/712 (0.6%)	11/863 (1.3%)	15/1 575 (1.0%)
60–69	7/508 (1.4%)	12/671 (1.8%)	19/1 179 (1.6%)
≥70	2/334 (0.6%)	12/580 (2.1%)	14/914 (1.5%)
Total	16/3 268 (0.5%)	43/3 856 (1.1%)	59/7 124 (0.8%)

Table 4. Clinical arthritis in association with positive serology and X-ray changes

Cut-off level of RF-positivity	Number of cases with			Total
	RF+ X-ray−	RF− X-ray+	RF+ X-ray+	
Latex screening	21	12	38	71
Latex 2nd dilution	16	16	34	66
Waaler-Rose 32	13	23	27	63

Table 5. Rheumatoid factor-positivity and X-ray changes in patients with "definite" and "probable" arthritis

Combinations		Cases with arthritis		
RF	X-ray	"Definite"	"Probable"	Total
−	Not taken	1% (1)	5% (7)	6% (8)
−	−	15% (21)	28% (38)	43% (59)
+	−	10% (14)	5% (7)	15% (21)
−	+	7% (10)	1% (2)	9% (12)
+	+	26% (36)	1% (2)	28% (38)
Total		59% (82)	41% (56)	100% (138)

the arthritis was graded as "definite." No Waaler-Rose positive cases were encountered among subjects with arthritis not defined as RA.

The latex slide test was positive for all but two of the arthritis cases positive in the Waler-Rose test and for 19 cases negative in it. Nine of these 19 cases were reactive only at the screening dilution. The total number of seropositive arthritis cases was 59, corresponding to a prevalence of 0.8% (0.5% in males and 1.1% in females). The prevalence increased progressively from 0.2% in the age group of 30–39 years to 1.6% in the age group of 60–69 years, whereafter it seemed to level off (Table 3).

Fifty subjects with clinical arthritis had radiological changes in hands compatible with RA. This corresponds to a 0.7% prevalence of clinical arthritis associated with radiological changes (0.4% in males and 0.9% in females). Minor radiological changes yet compatible with RA were recorded for 1.0% of females and for 0.4% of males without clinical arthritis.

Changes characteristic of erosive osteoarthrosis were recorded for 4% of the Waaler-Rose negative subjects without arthritis, for 3% of the Waaler-Rose positive subjects without arthritis, for 10% of the Waaler-Rose negative cases with clinical arthritis, but for none of the Waaler-Rose positive cases with clinical arthritis.

Table 4 gives the number of clinical cases associated with positive serology or with X-ray changes compatible with RA or with both. Data are presented separately for three different RF levels as cut-off points for positive reactions. Depending on the cut-off point, 63 to 71 subjects had clinical arthritis associated either with positive serology, or with radiological changes compatible with RA or with both.

As seen in Table 5, cases with radiological changes compatible with RA and those with positive RF reactions were concentrated in the group with "definite" arthritis. In only two seropositive cases with radiological RA changes was the arthritis graded as "probable." The great majority had a long-lasting disease which had led to marked joint destructions.

Twelve cases with radiological RA changes were entirely seronegative. Information collected from other sources revealed that three of these were seroconversion cases (two cases were known to have been positive at an earlier phase and one became positive later on). Two subjects had juvenile RA with the onset of disease at an early age. One case with disease predominantly affecting the large joints was known to be persistently seronegative. In five instances there was no information on earlier or later RF tests. In one of these cases the disease predominantly affected the large joints and one represented a burn-out case in which the disease had led to severe joint destruction. In one typical RA case, the seronegativity was based only on the Waaler-Rose test, as the latex test had no been performed.

Discussion

RA is a diagnosis made primarily on clinical grounds. Typical cases are no problem, but difficulties are encountered in finding a satisfactory definition of the full gradient of rheumatoid disease.

The detection of RFs is an important finding. Arguments have been presented for and against the

concept of seropositive RA as a disease of its own, distinct from seronegative RA [11–13]. About one-third of patients initially presenting with symptoms and signs compatible with RA are seronegative in conventional RF tests [14]. These patients obviously have some kind of inflammatory joint disease. Seronegative RA tends to run a more favorable course than its seropositive counterpart, and many patients go on to have a complete remission. Thus, one would expect that the relative proportion of seronegative RA cases encountered in cross-sectional surveys will be less than one-third. The reverse is true, however, since two-thirds or even more of cases in community surveys considered to have RA have shown seronegative findings. Seroconversion from positive at the initial presentation to negative at the time of the community survey may explain these findings in small part. It seems reasonable to assume, however, that a substantial proportion of cases with seronegative RA encountered in early population surveys did not have any inflammatory joint disease at all.

In the present work, the three main facets of the rheumatoid disease, clinical arthritis, radiological changes, and the occurrence of RFs, were assessed independently of each other. In terms of a prevalence study of RA, a uniform single-phase examination would have been better than our two-phase design. The Mini-Finland Health Survey, however, included other elements such as evaluation of various screening procedures. Therefore, two separate examinations seemed advisable. As a quality control, a random subsample was asked to come for reexamination irrespective of the screening results. No arthritis cases were found among the screening-negative persons.

To include atypical cases, we made no specifications for the pattern of joint involvement. Atypical cases, however, occurred very infrequently. The arthritis was graded as "definite" or "probable." It proved that cases with radiological changes typical of RA or with positive RF reactions were concentrated in the "definite" group. No correlation was observed between RF positivity and symptoms such as pain on motion or tenderness in joints separate from clinical arthritis (data not shown).

Radiographs were taken only of the hands. Since radiological erosions usually develop first in the feet, we obviously missed some early cases. In most cases, however, the disease was of long duration, thus allowing time for the development of changes also in the hands.

Minor changes compatible with RA were detected in 0.7% of subjects without clinical arthritis, more frequently in females than in males. Some of these cases probably represent the true gradient of RA. In population studies carried out by Lawrence and Kellgren in England, the prevalence of isolated positive X-rays was 1% [15]. Thus, the specificity of our radiological criteria was of about the same level as the specificity of criteria used earlier in England.

The prevalence of clinical arthritis corroborated by radiological RA changes in the Mini-Finland Health Survey was 0.7%, whereas the English figure was 0.9% [15].

The differentiation between seropositivity and seronegativity depends on the sensitivity of the RF assay. For a test to be acceptable, it is commonly considered that the frequency of positive reactions in the control population should not exceed 5%. The prevalence of "false-positive" RF reactions, however, increases with advancing age, and the age structure of the control populations varies. Moreover, there are geographical differences which can hardly be explained on the basis of methodological issues.

Our Waaler-Rose test yielded somewhat fewer "false-positive" reactions than the test used in prevalence studies in England, whereas our latex test with the screening dilution as the cut-off level gave appreciably more positive results. The second dilution step in our latex test (about 40 IU/ml according to the manufacturer) fairly closely corresponds to the cut-off level of the Waaler-Rose test used by Lawrence and Kellgren (on the basis of the tests performed on the matched controls; data not shown). With this level as the criterion for seropositivity the prevalence of seropositive arthritis in the Mini-Finland Health Survey was 0.7%. The corresponding figure for England was 1.0% [13].

The Mini-Finland Health Survey covered the population 30 years of age or older, whereas the English study covered those aged 15 years or over. Since RA is a relatively rare disease in the age group 15 to 29 years, it seems that the prevalence in the Mini-Finland Health Survey of clinical arthritis associated with positive radiological or serological findings was appreciably lower, only about one-half of that found in England 20 years earlier.

From the biological point of view, it may be appropriate to have a sensitive RF assay. In our earlier cohort study of recent-onset arthritis, the initial positivity in the most sensitive assays (latex slide test and IgM-RF by enzyme immunoassay) was best able to distinguish between the erosive and nonerosive cases [16]. The present series included several cases with destructive disease reactive in the latex test only at the initial serum dilution. Twelve arthritis cases with radiological RA changes were negative even at that dilution. The group included

seroconversion cases and rheumatoid variants typically seronegative, such as early-onset juvenile RA. In some instances there was no information on earlier or later RF tests. Thus, the true prevalence of seronegative destructive RA in our cross-sectional population survey is quite low.

The prevalence of seropositive RA in our series increased progressively from the ages 30–39 years to the ages 60–69 years. One might expect to find, however, only a modest nonprogressive increase in prevalence, since, at least according to our experience, the age-specific incidence rates of RA do not vary greatly within the age range of 30 to 70 years [17], and seropositive RA is associated with increased mortality. The excess in the older age groups of arthritis cases who frequently had quite a severe disease may reflect either a higher incidence of seropositive arthritis earlier on or a higher rate of complete remissions nowadays. There is indeed evidence from different sources that the incidence of RA has decreased [18] and that the disease has become less severe [19].

A prevalence study of RA dealing with a population sample aged 15 years and over was carried out in 1957–1958 in Heinola, Finland [20]. Among the 539 persons examined, there were four seropositive cases fulfilling the American Rheumatism Association's criteria for definite RA and five seropositive cases fulfilling the criteria for probable RA [21]. Two subjects, both seropositive, were severely handicapped by the disease. In this study, one-half of the cases positive in the Waaler-Rose test had either definite or probable RA [21], whereas in the present series only one-quarter of the Waaler-Rose positive cases had clinical arthritis. In spite of differences in the presentation of data, the findings are at least compatible with the contention that the prevalence of RA is decreasing.

The significance of seronegative nonerosive arthritis encountered in cross-sectional population surveys remains to be settled, but most cases may not represent RA. On the other hand, we propose that clinical arthritis associated either with positive serology or with typical radiological changes or both is a useful measure of the occurrence of RA in this type of study. Cases in complete remission will be missed, but there will hardly be any way to find these in cross-sectional surveys.

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