Pattern of rheumatoid arthritis in West Malaysia

From the Departments of Medicine, Orthopaedic Surgery, Radiology and Pathology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

Common diseases are subject to considerable variation in incidence and expression due to influence of geographical factors, and rheumatoid arthritis (RA) is an example of this. Greenwood (1969) indicated that RA in tropical Africa is more benign than in temperate climates. In West Malaysia the severity and incidence appear to be intermediate between that in tropical Africa and in the temperate zones. Environmental, ethnic, and social factors interact in determining the pattern. Furthermore, the condition occurs at equivalent incidence with other rheumatic disorders, particularly gout and autoimmune disease as systemic lupus erythematosus (SLE). This report is a study of RA in the three main ethnic groups in West Malaysia.

Material and methods

The 57 patients attended the Arthritis Clinic, University Hospital, Kuala Lumpur, during 1967–70 and satisfied American Rheumatism Association criteria of 'definite' RA (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959). A further 21 cases of 'probable' RA have been excluded.

Joints

In the clinical assessment, the joints were examined according to the method of Beetham, Polky, Slocomb, and Weaver (1965).

Laboratory investigations

(1) Haematology (Dacie and Lewis, 1968).
(2) Urine analysis.
(3) Stool for ankylostomiasis.
(4) Serum proteins, uric acid, and blood urea.
(5) Serology: Waaler-Rose, latex-fixation for rheumatoid factor (RF, Hyland), antistreptolysin-O titre (Difco), LE cell, and blood Kahn tests.

The Waaler-Rose test was done according to the method of Dacie and Lewis (1968). The latex-fixation test with human gamma-globulin for RF was performed on a 1 in 20 serum dilution as a slide screen at room temperature (ca. 25°C), and positive sera inactivated by heating at 56°C for 30 min. (Dequeker, Van Noyan, and Vandepitte, 1969) and titrated on slides. The LE cell test was performed by the method of Zinkham and Conley (1956), with 80 x 12 mm. heparinized plastic tubes containing 8 ml. blood and twelve glass beads of 2–3 mm. diameter, rotated at 33 r.p.m. for 20 min. and then maintained at room temperature for 20 min. before separation of the buffy coat.

(6) Radiology of hands, chest, and all involved joints.
(7) Electrocardiogram.
(8) Synovial biopsy.

Social background

Of the patients with definite RA, the male patients were predominantly semi-skilled and unskilled workers. Most of the females were housewives from similar social groups, less than one-third coming from a skilled working background, and four were from professional families. Two-thirds of the patients were from Kuala Lumpur, and most of the remainder from provincial towns, with only four from rural areas.

Controls

Blood and serum samples were obtained from medical students and the inhabitants of various rural and semi-rural areas.

Results

Table I shows the number of patients with RA. Compared with other joint conditions, RA and gout provided the majority of patients. Data on rheumatic fever, and septic, tuberculous, and post-traumatic arthritis have been excluded. Out of 53 patients with SLE seen during the period of this study, 35 had joint symptoms (Table I, overleaf).

Of the 57 patients with definite RA, 27 were Chinese, 17 Indians, and 13 Malays (Table II). Female preponderance was noted in all three ethnic groups, the overall ratio being 4:2:1. The age at onset is shown in Fig. 1. In most patients the illness started when they were between 26 and 65 years. At presentation they had been ill for periods from a few weeks to 21 years: 29 for up to 1 year, seventeen for 2 to 5 years, and eleven for more than 5 years. A history of morning stiffness was given in almost all instances.
Activity  
Inactive  
Table  
presentation  
at  
between Scots,  
Functional grade  
Race  
Scottish  
grading  
Functional  
in  
fourteen  
phalangeal joints  
noted fairly commonly  
The  
joints  
geal, ankle,  
interphalangeal,  
FIG.  
1  
Articular manifestations  
Acute  
tropical  
Ankylosing arthritis  
Polyarthralgia  
of  
disease  
Still's  
Systemic lupus  
62  
Gout  
Rheumatoid arthritis  
Definite  
seen  
Table I  
1967 to 1970  
152 Annals of the Rheumatic Diseases  
5.0  
.0  
4)  
ES  
u  
10  
1.0  
26 32 40  
241  
No. of  
Patients  
Rheumatoid arthritis  
Definite  
Probable  
Gout  
Systemic lup erythematosus with joint  
symptoms  
Polyarthralgia of unknown aetiology  
Still's disease  
Acute tropical polyarthritis  
Psoriatic arthritis  
Ankylosing spondylitis  
Total  
Table II  
Patients with definite rheumatoid arthritis  
distributed by ethnic group and sex related to total  
hospital admissions, 1967–1970  
Race  
Sex  
No. of  
admissions  
Ratio of cases  
to admissions  
Male  
Female  
Total  
Chinese  
4  
23  
27  
20,217  
1:749  
Indians  
3  
14  
17  
9,621  
1:566  
Malays  
4  
9  
13  
5,408  
1:416  
Total  
11  
46  
57  
35,246  
1:618  
FIG. 1 Age of patients with definite rheumatoid arthritis on  
presentation at the hospital  
Articular manifestations  
The joints most frequently involved were wrist,  
proximal interphalangeal, knee, metacarpophalan-  
geal, ankle, and elbow. Spindling of the fingers was  
noted fairly commonly where the proximal inter-  
phalangeal joints were involved, and hand deformities  
in fourteen cases. There were no significant differences  
between the three ethnic groups. The functional grade  
and activity of arthritis is compared with Scottish  
(Duthie, Thompson, Weir, and Fletcher, 1955) and  
Nigerian (Greenwood, 1969) patients in Table III.  
Extra-articular manifestations  
No rheumatoid nodules were seen in this series. Small  
subcutaneous nodules just distal to the olecranon in  
three patients were fibro-fatty tissue on biopsy.  
Hepatomegaly occurred in ten patients, with one  
in congestive cardiac failure, splenomegaly in five,  
and palpable cervical lymph nodes in one. Fever was  
usually absent, and mild when present. Systemic RA  
(Schmid, Cooper, Ziff, and McEwen, 1961) occurred  
in a Chinese patient with digital vasculitis and  
gangrene of the finger tips and toes, mixed sensori-  
motor neuropathy with wrist and foot drop, peripheral  
carditis, episcleritis, and scleromalacia perforans.  
Associated diseases  
Five patients had ankylostomiasis with anaemia.  
Three others were diabetics, and eight were hypertensive.  
Two post-menopausal females had ischaemic  
heart disease. Two patients had Bell's palsy, two  
bronchial asthma, one pulmonary tuberculosis, and  
one glaucoma. No clinical or laboratory evidence of  
malaria was encountered.  
Haematological investigations  
Haemoglobin values ranged from 4.0 to 15.5 g. per  
100 ml. (mean 11.6). Eleven had values less than 10.1  
g. per 100 ml., three having ankylostomiasis. The  
total white cell count ranged from 4,000 to 19,500 per  
µl. (mean 7,900), neutrophils 2,600 to 15,600 per µl.  
Table III Percentage distribution of functional class and activity at the time of presentation. A comparison  
between Scots, Nigerians, and Malaysians  
Functional grading and activity according to Duthie and others (1955).  
Race  
Scottish  
(Duthie and others, 1955)  
Nigerian  
(Greenwood, 1969)  
Malaysian  
Functional grade  
I  
II  
III  
IV  
Inactive  
10  
67  
32  
Moderately active  
63  
25  
56  
Very active  
26  
24  
40  
Total  
241
(mean 5,200). The erythrocyte sedimentation rate (Westergren) varied from 5 to 139 mm. in one hour (mean 73). No significant differences occurred between the three ethnic groups.

Biochemical investigations
The distribution of serum albumin in 48 patients and of serum gamma globulin in 26 is shown in Fig. 2 as compared with normal students. One patient had a cryoglobulin fraction (IgM). Serum uric acid was determined in 51 patients; nine had marginally raised values ranging from 6-1 to 9-3 mg. per 100 ml., one being in chronic renal failure. Mean blood urea in fifty patients was 27 mg. per 100 ml. In forty patients mean serum iron (80 μg. per 100 ml.) and percentage iron saturation (25 per cent.) were low, although the mean unsaturated iron-binding capacity (237 μg. per 100 ml.) and total iron-binding capacity (317 μg. per 100 ml.) were within normal limits. The mean serum folic acid was 7-6 ng. per ml., but ranged from 3-4 to 26. Mean serum vitamin B₁₂ level was normal at 685 pg. per ml.

![FIG. 13: Indians, Chinese, and total (47) patients with rheumatoid arthritis.](image)

Immunological investigations
The results of Waaler-Rose, latex fixation for RF, and LE cell tests are shown in Table IV. A clinically significant positive Waaler-Rose test was taken as a titre of 1:32 or more, and latex fixation as 1:160 or more. The proportion of positive results for RF and the LE cell test in the Chinese was greater than for the other ethnic groups. Antistreptolysin-O titres ranged from 50 to greater than 2,500 Todd units (mean 370) for 32 patients with RA. The blood Kahn test in 32 instances was negative.

No positive Waaler-Rose test was encountered in 66 medical students. In a group of 81, one positive latex-fixation test (1:320 after heating) was obtained (1-2 per cent.). The antistreptolysin-O titres ranged from 12 to 250 in 32 normal students and blood donors (mean 106). In a group of forty rural and semi-rural individuals of the various races, aged 11 to 61 years (mean 31), no positive Waaler-Rose test was encountered. The latex test was positive at a 1 in 20 dilution in two, and at 1 in 40 in one individual, but no higher titres were found. The antistreptolysin-O titres ranged from 50 to 625 Todd units (mean 245). The total serum globulins ranged from 2-7 to 6-2 g. per 100 ml. (mean 4-2). Malaria is a common infection in the area from which these individuals were drawn.

Radiological studies of joints
Radiological grading of hands (Kellgren, Jeffrey, and Ball, 1963) was available in 49 patients. 88 per cent. were divided equally between Grades 0–1 and 2, with 10 per cent. in Grade 3, and 2 per cent. in Grade 4. Greenwood (1969) found a similar preponderance of less severe changes, in contrast to the English series of Thould and Simon (1966) with which he compared them. No significant differences were noted between the three main ethnic groups in Malaysia. Erosions were seen most commonly in the metacarpophalangeal and proximal interphalangeal joints and in decreasing order of frequency in the bases of the metacarpals, ulnar styloid, and lower end of ulna. Bony ankylosis involving the wrists, carpus, and carpometacarpal joints were seen in three Chinese and one Indian. Radiography of the sacroiliac joints suggested chronic inflammatory change in one out of 21 examinations.

<table>
<thead>
<tr>
<th>Race</th>
<th>Waaler-Rose test</th>
<th>Latex-fixation test</th>
<th>LE cell test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. tested</td>
<td>Positive &gt; 1:32</td>
<td>No. tested</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------</td>
<td>-------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Chinese</td>
<td>24</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indians</td>
<td>13</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malays</td>
<td>10</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>47</td>
<td>9</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Synovial histopathology
This was obtained in eleven patients (four synovial biopsies and seven synovectomies). Proliferative changes were seen in all, with synovial hyperplasia, villous formation, and infiltration by polymorphs, lymphocytes, mononuclear, and plasma cells, consistent with chronic nonspecific synovitis; they were rather uniform in seven cases, but more severe in two, with presence of fibrinoid necrosis in one, and mild in another two.

Discussion
Rheumatoid arthritis is not an uncommon disease in West Malaysia, and together with gout is a major cause of joint disability.

The age distribution shows the majority in the 26 to 65 year range. In West Nigeria (Greenwood, 1969) there was preponderance of younger patients (21 to 40 years) and no distinct sex predominance. Our patients were predominantly female as in British (Kersley, 1962) and Japan (Schichikawa, 1968). The distribution of RA does not differ significantly among the three main ethnic groups. Unlike the situation in the United Kingdom (Sze, 1963) with most of the patients being over the age of 45, more than half our cases are below this age. This may be related to the marked preponderance of younger people in the population (Vital Statistics, West Malaysia, 1968), who are exposed to the tropical environment where multiple infections are common. Whereas Greenwood (1968) encountered relatively few cases of SLE in Western Nigeria, 53 cases were seen here during the period of study; these will be reported in a separate paper.

The frequency of RA, with one case in 618 hospital admissions, appears higher than in tropical West Africa, where Greenwood (1969) found an incidence of only 1 in 2,344 admissions over a 10-year period. This may be due partly to the tendency for patients with a chronic disease to seek treatment at a new hospital. Nonetheless the incidence is lower than in the United Kingdom, where Sze (1963) found an incidence of 1 in 125 of total hospital discharges and deaths from all causes, based on the 1957 hospital inpatients' inquiry. Figures from general practice indicate a higher incidence in the general population of the United Kingdom, increasing with age (Sze, 1963; Lawrence, 1963). In the Osaka district in Japan, Schichikawa (1966) reported RA in 1 in 167 of the 45 to 64 age group. Articular manifestations were marked by a good deal of functional disability (Table III), although radiological changes were mild. About half of the patients had had the disease for 2 to 21 years before attendance.

In contrast to a 30 per cent. incidence in a British series (Thompson, 1965), subcutaneous rheumatoid nodules were not seen. Chest x rays revealed no rheumatoid lung disease. Splenomegaly was occasionally found, but malaria is still common in Malaysia. Visceral manifestations of RA were seen in two Chinese females.

The incidence of positive Waaler-Rose and latex-fixation tests was low in controls of medical students and rural subjects. Lim and Leong (1967) found an incidence of 2.3 per cent. of positive Waaler-Rose tests in 798 urban Malaysians, and in about one-third of the seropositive individuals clinical evidence of arthritis was found. Our patients with RA showed a higher proportion of positive results (Waaler-Rose 19 per cent. positive and latex fixation 33 per cent. positive). Heterophil antibodies against sheep red cells are rarely encountered here, and the Waaler-Rose test appears suitable for the detection of RF. Greenwood, Muller, and Valkenburg (1971) have shown that, in Nigeria, where heterophil antibodies are encountered frequently at high titre, the human erythrocyte agglutination test is more reliable. In the apparently normal Nigerian population, Valkenburg (1963) and Greenwood (1969) found a high incidence of positive latex-fixation tests, and the latter commented that this test might have limited diagnostic value. RF with selective affinity for human gamma globulin is prevalent at high titre in the older Nigerian population (Greenwood and others, 1971), which may result from the cumulative effects of a variety of infections rather than from malaria alone. Curtain, Kidson, Champness, and Gorman (1964) have stressed the role of cumulative, multiple infections in the causation of high gamma globulins in New Guinea, and the interpretation of positive tests for RF should be made with caution in that region (Wells, 1967). Our own experience with rural Malay-Asian populations, where malaria is quite a common infection, is consistent with these views. Even in temperate zones, the significance of serological tests in population studies is difficult to evaluate (de Graaff, Laine, and Lawrence, 1963; Hijmans, 1963; Valkenburg, 1963), although Glynn (1968) gives an incidence of only 2 to 5 per cent. of positive reactions for RF in non-rheumatoid subjects, and Duthie (1969) finds 85 per cent. of positive reactions in established RA. The complexity of the pattern of disturbed immunoglobulin production in RA has been reviewed by Waller (1971).

LE cell tests were positive in 14 per cent. in this series. The significance in RA has been reviewed by Duthie (1969), and he indicated that such cases were not necessarily more likely to develop frank SLE. The ultimate course of the RA may be more severe, however, in those cases showing positive tests for LE cells (Hazevoet, Hijmans, and Kievits, 1966) and antinuclear factor (Duthie, 1969).

Trowell (1960) found raised serum gamma globulins and erythrocyte sedimentation rates in apparently normal African communities, and Tint (1971)
reported occasional high ESR values in otherwise healthy Burmese, especially females; our experience with medical students is similar. Saha and Banerjee (1971) found a positive correlation of ESR with globulin level, especially the gamma globulins, which could be a factor in causing high ESR in the tropics.

The anaemia of RA is usually normocytic, hypochromic, with lowered serum iron, TIBC, and transferrin saturation, but decrease in marrow sideroblasts and normal or increased reticulo-entheilial iron (Cartwright and Lee, 1971). The overall pattern of our anaemic patients conforms to this. Gough, McCarthy, Read, Mollin, and Waters (1964) found that patients with RA may develop megaloblastic anaemia through deficiency of, or increased requirements for, folate. Nine out of 37 of our patients had serum folate levels below 5 ng per ml., and in three with haemoglobin levels below 10 g. per 100 ml. both iron and folate values were low.

Greenwood (1968) suggested that the benign nature of tropical rheumatoid arthritis may be related to immunological changes induced by parasites, particularly malaria. However, SLE is particularly common in the Chinese here, and Tay and Khoo (1970, 1971) have found the same in Singapore. The serological changes (RF and LE cells) are also more frequent in the Chinese, suggesting that both genetic and environmental factors may influence the disease.

Summary

In West Malaysia RA appears to be less common than in temperate climates, but more common than in tropical Africa; furthermore, the incidence of gout and SLE is comparable. The clinical manifestations of RA are milder than those seen in more temperate climates. Subcutaneous rheumatoid nodules have not been observed.

Positive serological tests for RF are significantly higher than in the general Malaysian population, but still lower than those reported for patients with RA in temperate climates. Of the three main ethnic groups, the highest incidence of positive results is found in the Chinese.

We thank Dr. H. O. Wong, Head of the Department of Medicine, Professor J. F. Silva, Head of the Orthopaedic Department, Mr. G. L. Chan, F.I.M.L.T., and Mr. K. H. Yee and the staff of the Nutritional Anaemia Research Laboratory, for co-operation and assistance; the General Manager and Dr. B. Freeman of Pahang Consolidated Co. Ltd., Sungei Leeming, for facilities to obtain control blood samples. This study was supported in part by funds from the United States Public Health Service Grant AM11048. One of us (J. C. W.) is in receipt of a Special Commonwealth Award.

References


Greenwood, B. M. (1968) Lancet, 2, 380 (Autoimmune disease and parasitic infections in Nigerians)


