

RHEUMATOID ARTHRITIS IN SINGAPORE A CLINICAL STUDY

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SYNOPSIS

Geographical difference in the incidence of rheumatoid arthritis (RA) has been observed. The disease, for instance is rare in tropical Africa and runs a more benign course than in temperate climates.

Over the past 9 years in Singapore (1965 to 1974), 190 cases of classical and definite RA (5 or more A.R.A. criteria) were found—an average of one such case in 245 new hospital admissions or 21 new cases seen every year.

The local incidence is higher than those reported from Africa and West Malaysia but it is lower than those found in England, United States or Japan.

Of the three major ethnic groups in this country, Chinese were the most commonly affected (70.5%). Most victims were females, usually housewives, in their third to fifth decade of life. Half of the patients in this series had the arthritis for one to 20 years (an average of 3 years). Except for the knee joints, most patients had peripheral joint involvements, a clinical pattern different from that seen in Nigeria.

Extra-articular manifestations and systemic complications were not as common as those found in Western centres. Radiological findings too, revealed low incidence of erosive arthropathy. Only 41% were sero-positive and these occurred in older patients with longer duration of the illness.

The majority of the cases improved with oral salicylates. Short courses of oral corticosteroids were used in 51%. Only 2% received immunosuppressive drugs. The prognosis on the whole is better than that reported from the temperate countries. Of the 10 deaths found in the 9 years, only two perished from the rheumatoid process.

The lower incidence and the more benign course of RA in this study confirm previous observations reported in other tropical countries.

INTRODUCTION

In spite of world wide intensive research, rheumatoid arthritis (RA) remains a disease of unknown origin. Though the presenting symptoms and signs are predominantly a joint problem, it can affect many body systems, and thus the term "rheumatoid disease" was coined (Ellman and Ball, 1948).

Attempts to prove an infective basis for the disease have not been successful. However, changes in the immune mechanism have been consistently found (Herdberg, 1965; Schubart *et al*, 1965; Zvaifler, 1969).

In temperate countries, RA is a very common disease affecting mainly women from the third to seventh decade of life. In North America, for instance, the prevalence rate in the population ranged from 0.5 to 3.8% in women and from 0.15 to 1.3% in the men (Gilliland and Mannik, 1974)..

In Scotland, 94 new cases were found annually (Duthie *et al*, 1955), but in Western Nigeria, only 77 cases were discovered over a ten-year period (Greenwood, 1969). Reports from other parts of Africa, such as Malawi, Uganda and Kenya confirmed the rarity of RA in this areas (Goodall, 1956; Sharper and Sharper, 1958; Hall, 1966). Besides, the disease there was found to be more benign.

Recent survey in Malaysia revealed that RA is not uncommon in that country and the incidence is intermediate between that found in the temperate countries and that reported in tropical Africa (Toh *et al*, 1973).

It appears therefore, that some geographical differences do exist in the incidence and clinical pattern of RA. Since no study has been carried out in Singapore, a retrospective study of 190 cases with classical and definite RA was carried out from 1965 to 1974. The results obtained are compared with other published series and discussed.

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PATIENTS AND METHODS

Between 1965 to 1974 inclusive (9 years), 221 adult patients diagnosed as rheumatoid arthritis

(RA) by the American Rheumatism Association criteria (Ropes, 1959) at the Department of Medicine, Singapore General Hospital were analysed. Classical and definite RA were found in 190 patients and they were studied. Excluded were the 'probable' or 'possible' cases.

Personal data, detailed history and careful physical examination were carried out when the patients were first admitted, and later, at subsequent follow-up in the outpatient department.

The site, disease activity and functional capacity of the joint lesions were recorded and assessed by the criteria described by Duthie *et al* (1955). Radiological examination of the affected joints were graded according to Kellgren (1957). Laboratory investigations done included full haematological and urinary examination, ESR, serum proteins, rheumatoid arthritis factor (RA factor) using the method described by Dacie and Lewis (1968), L.E. cells, antinuclear antibody, anti-streptococcal O titre, VDRL, ECG, and others. Associated medical conditions as well as systemic complications from RA noted during the course of the disease were investigated whenever indicated.

Patients were treated initially with oral salicylates and the response observed. Failure to respond to salicylates after an adequate time and dosage demands other drugs such as paracetamol, indomethacin, phenylbutazone, codeine, ketoprofen, flufenamic acid, ibuprofen, and others. In severe cases resistant to the above drug, oral or parenteral steroid, oral penicillamine, gold salts, and even cyclophosphamide were considered. Side-effects from drugs were monitored.

At the end of 1974, the prognosis of the 190 patients was determined.

RESULTS

During the 9-year period, 221 cases of Rheumatoid arthritis (RA) were diagnosed, of which 190 were found to be classical and definite RA, 21 were probable RA and 10, possible RA.

Detail study of the classical and definite RA shows that there was a gradual increase of cases over the past 6 years and the average annual number of new cases found was 21. The ratio of new cases to new hospital admissions per year was 1: 245 (Tables Ia and b).

The race, sex and age distributions of the 190 classical and definite RA are shown in Table II. Majority were Chinese females between the ages of 21 to 60. Mean age for all males was 30.7 years and for all females, 46.2 years. Majority of affected females (134 cases) were housewives (83 cases), the others were professionals (16), unskilled workers (13), semi-skilled workers (12) and students (10). Of the 56 males, majority were servicemen and students (23 cases), and the others were unskilled labourers (15), semi-skilled workers (11) and professionals (7).

Table III shows the duration of the arthritis

TABLE I

(a) NUMBER OF NEW CASES OF CLASSICAL AND DEFINITE R.A. SEEN PER YEAR

| Year | No. Cases | No. Hospital Admissions |
|-------------|-----------|-------------------------|
| 1965 | 2 | 1,516 |
| 1966 | 3 | 2,537 |
| 1967 | 7 | 4,141 |
| 1968 | 8 | 4,671 |
| 1969 | 26 | 5,132 |
| 1970 | 15 | 5,251 |
| 1971 | 27 | 5,906 |
| 1972 | 26 | 5,718 |
| 1973 | 38 | 5,503 |
| 1974 | 37 | 6,233 |
| Total Cases | 190 | 46,606 |

Average cases per year = 21

TABLE I

(b) RATIO OF NEW R. A. CASES TO NEW HOSPITAL ADMISSIONS—A COMPARISON

| | |
|-----------|-----------------------------|
| England | 1 : 125 (Sze 1963) |
| Japan | 1 : 167 (Shichikawa, 1966) |
| Singapore | 1 : 245 (Tay, 1975) |
| Malaysia | 1 : 618 (Toh, 1973) |
| Africa | 1 : 2,344 (Greenwood, 1969) |

when first seen. The average duration for females was 3.5 years and that for males was 1.9 years.

Positive family history of RA was obtained in 7 cases—4 with affected siblings, 2 with affected parents and one, with affected offsprings.

Table IV (a, b and c) shows the incidence of the sites of joint involvement, the disease activity and the functional activity of these joints on admission, and Table V lists the extra-articular findings of the 190 cases.

Significant laboratory investigations are shown in Table VI. Radiological gradings of the affected joints and the chronicity of the RA disease in the seropositive and seronegative cases are shown in Table VII (a) and (b) respectively. Severe radiological changes with bony erosions and deformities were uncommon (12.1%). Most sero-positive cases had longer duration of the disease. Of the 190 cases, 176 (92.6%) were treated with oral salicylates at one time or another, and in the usual recommended dosage. Systemic steroids usually in short courses were given to 97 cases (51.1%) often in combination of other drugs. Other anti-inflammatory drugs used were Indomethacin (62 cases or 32.6%), Phenylbutazone (45 cases or 23.6%) and more recently Penicillamine (15 cases or 7.8%). Only 7 cases needed gold salts

TABLE II
RACE, SEX AND AGE DISTRIBUTIONS
(190 cases)

| Age | Chinese | | Malays | | Indians | | Others | | Total |
|-------------------------|------------|-----|-----------|----|-----------|----|---------|---|-------------|
| | M | F | M | F | M | F | M | M | |
| Under 20 Yrs. | 14 | 10 | 2 | 0 | 4 | 2 | 0 | 0 | 32(16.8%) |
| 21—40 Yrs. | 12 | 29 | 2 | 7 | 2 | 4 | 0 | 1 | 57(30.0%) |
| 41—60 Yrs. | 6 | 40 | 4 | 8 | 8 | 5 | 0 | 1 | 72(37.9%) |
| 61 and above | 1 | 22 | 0 | 4 | 1 | 1 | 0 | 0 | 29(15.2%) |
| Total Cases | 33 | 101 | 8 | 19 | 15 | 12 | 0 | 2 | 190(100.0%) |
| Total M and F Cases (%) | 134(70.5%) | | 27(14.2%) | | 27(14.2%) | | 2(1.1%) | | |

Whole Series

Males = 56 cases Female = 134 cases

M : F Ratio = 1 : 2.4

TABLE III
DURATION OF DISEASE WHEN FIRST SEEN

| Duration | Males | Females | Total (%) |
|------------------------|-------|---------|-------------|
| Less than 1 month | 18 | 31 | 49(25.8%) |
| 1 month to 1 year | 17 | 27 | 44(23.1%) |
| 1 year to 5 years | 10 | 44 | 54(28.4%) |
| 5 years + to 10 years | 9 | 20 | 29(15.3%) |
| 10 years + to 20 years | 2 | 12 | 14(7.3%) |
| Total cases | 56 | 134 | 190(100.0%) |

TABLE IV
(a) SITES OF JOINT INVOLVEMENT

| Peripheral Joints | Males | Females | Total (%) | Nigerian Series (%) |
|---|-------|---------|------------|---------------------|
| Metacarpophalangeal Jt | 42 | 101 | 143(75.2%) | 51% |
| Proximal Interphal. Joint | 37 | 101 | 138(72.6%) | 59% |
| Wrist Joint | 44 | 94 | 138(72.6%) | 72% |
| Ankle Joint | 35 | 93 | 128(67.4%) | 69% |
| Metatarsophal. and Intertarsophal. Joints | 16 | 41 | 57(30.0%) | 24% |
| Central Joints | | | | |
| Knee Joint | 48 | 100 | 148(77.9%) | 61% |
| Elbow Joint | 25 | 51 | 76(40.0%) | 44% |
| Shoulder Joint | 22 | 50 | 72(37.9%) | 18% |
| Hip Joint | 13 | 24 | 37(19.5%) | 4% |
| Other Joints | | | | |
| Cervical Spine | 4 | 22 | 26(13.6%) | 18% |
| Sternoclavicular Joint | 5 | 17 | 22(11.6%) | — |
| Temporomandibular Joint | 4 | 17 | 22(11.6%) | 3% |
| Sacroiliac Joint | 2 | 3 | 5(2.6%) | — |

TABLE IV
(b) DISEASE ACTIVITY ON ADMISSION
(According to Duthie, 1955)

| | Grade 1 | Grade 2 | Grade 3 |
|--------------------------------------|---------------|---------------|------------|
| | (Very active) | (Mod. active) | (Inactive) |
| Present Series | 38.9% (74) | 48.9% (93) | 12.2% (23) |
| Malaysian Series (Toh, 1973) | 40.0% | 56.0% | 4.0% |
| Nigerian Series (Greenwood, 1969) | 32.0% | 67.0% | 1.0% |
| Scottish Series (Duthie, 1955) | 26.0% | 63.0% | 10.0% |

TABLE IV
(c) FUNCTIONAL CAPACITY ON ADMISSION
(According to Duthie, 1955)

| | | | | |
|--------------------------------------|-----------|------------|------------|------------|
| Present Series | 8.9% (17) | 42.1% (86) | 35.3% (67) | 13.7% (26) |
| Malaysian Series (Toh, 1973) | 14.0% | 20.0% | 25.0% | 41.0% |
| Nigerian Series (Greenwood, 1969) | 6.0% | 28.0% | 44.0% | 22.0% |
| Scottish Series (Duthie, 1955) | 0.0% | 35.0% | 43.0% | 22.0% |

TABLE V
(a) EXTRA-ARTICULAR FINDINGS

| | Cases (%) |
|------------------------|------------|
| Pyrexia | 72 (37.9%) |
| Severe Anaemia | 26 (13.7%) |
| Hepato-Splenomegaly | 15 (7.8%) |
| R. A. Nodules | 9 (4.7%) |
| Lymphadenopathy | 6 (3.1%) |
| Malignant form of R.A. | 6 (3.1%) |
| Raynaud's Phenom. | 5 (2.6%) |
| Vasculitis | 5 (2.6%) |
| Episcleritis | 5 (2.6%) |

TABLE VI
INVESTIGATIONS

| | Cases (%) |
|--|------------|
| Haemoglobin | |
| 15 to 12 Gm / 100 ml | 72 (37.8%) |
| 12 to 9 Gm/100 ml | 83 (43.6%) |
| Less than 9 Gm/100 ml | 26 (13.6%) |
| Leucocytosis | |
| Above 10,000/cmm | 55 (28.9%) |
| E.S.R. | |
| Less than 20 mm/Hr (Westergreen) | 31 (16.3%) |
| 21 to 80 mm/Hr | 71 (37.3%) |
| 81 to 150 mm/Hr | 83 (43.6%) |
| Positive R.A. (1 : 32) | 78 (41.1%) |
| Positive L.E. cells | 3 (1.6%) |
| Positive VDRL | 3 (1.6%) |
| Serum Globulin above 3.5 Gm/100 ml | 65 (34.2%) |
| A.S.O.T. (higher than 200 Todd Units) | 40 (21.1%) |

and 5 intractable cases were treated with systemic cyclophosphamide.

Complications from treatment as well as from the RA are listed in Table VIII. Gastrointestinal bleeding from ulcerogenic drugs remains one of the most common complications in the treatment of the disease.

Of the 190 cases, 57 (30%) were followed up for one to two years and 34 (17.8%) for 2 to 8 years. The rest (99 cases or 52.2%) were followed up for under 6 months. They were either discharged to the outpatient clinics or to their own doctors.

Prognosis of the 190 cases revealed that 117 cases (61.6%) had improved when they were last seen by us. This was based on clinical and biochemical findings. In 20% (38 cases) no significant im-

provement or deterioration was noted. Periods of exacerbations and remissions were still encountered in spite of chemotherapy and physiotherapy. Twenty five cases (13.1%) showed slow progression of the joint and systemic lesions even with treatment. There were 10 deaths in this series. Eight died from unrelated diseases such as hypertensive cardiac failure (3 cases), cerebral thrombosis (2 cases) septicaemia (2 cases) and carcinoma of the lung (1 cases). Only two cases perished from fulminating rheumatoid process.

TABLE VII
(a) RADIOLOGICAL GRADING
(According to Kellgren, 1957)

| | Sero-positive (78 cases) | Sero-negative (112 cases) | Total Cases |
|-----------|-----------------------------|------------------------------|-------------|
| Grade 0 | 18 | 53 | 71(37.3%) |
| Grade I | 17 | 22 | 39(20.5%) |
| Grade II | 9 | 16 | 25(13.2%) |
| Grade III | 17 | 15 | 32(16.8%) |
| Grade IV | 17 | 6 | 23(12.1%) |

TABLE VII
(b) CHRONICITY OF DISEASE

| | Sero-positive (78 cases) | Sero-negative (112 cases) | Total Cases |
|---------------|-----------------------------|------------------------------|-------------|
| Under 1 year | 32 | 62 | 94(49.5%) |
| 1 to 5 years | 24 | 33 | 57(30.0%) |
| 5 to 20 years | 22 | 17 | 39(20.5%) |

TABLE VIII
COMPLICATIONS

(A) From Treatment (Cases)

| | |
|---------------------------------|----|
| Bleeding gastrointestinal tract | 15 |
| Drug rash | 7 |
| Alopecia | 7 |
| Myopathy | 6 |
| Steroid osteoporosis | 6 |
| Steroid cataract | 6 |
| Recurrent infections | 6 |
| Aseptic necrosis | 5 |
| Dwarfism | 4 |
| Drug hepatitis | 3 |

(B) From Rheumatoid Disease (Cases)

| | |
|-------------------------|----|
| Depression | 10 |
| Sjogren syndrome | 7 |
| Carpal tunnel syndrome | 5 |
| Uveitis | 4 |
| Pleural effusion | 4 |
| Spinal cord compression | 3 |
| Ruptured Popliteal cyst | 2 |
| Pericarditis | 2 |
| Aortitis | 1 |

DISCUSSION

For a long time, rheumatoid arthritis (RA) was regarded as an uncommon disease in Singapore and no attempt has been made to study the disease locally. This impression however, is not true as shown by the present study. Although there are no

previous records available for comparison, the local incidence of this condition appears to be on the increase. From 2 new cases in 1965, the number of new cases found in this department, rose sharply to 37 in 1974. Of the 221 cases of RA found in the 9-year period, 190 had the classical and definite forms and they were the subject of study in this paper. The local incidence therefore, is 21 new cases a year or one such case to every 245 new hospital admissions.

We believe that the real incidence in the Singapore population is much higher than the hospital figures since only the very acute or severe cases were admitted. Many mild cases were not registered as these were generally treated by their own doctors, by chemists, sinseh, bomohs and even by acupuncturists in town. The increased incidence of RA is attributed partly to the general awareness of the disease in Singapore, the availability of laboratory investigations and the frequent employment of other diagnostic procedures such as arthroscopy and synovial biopsy. The emergence of RA as one of the major causes of joint disability in recent years was noted to correspond to the rapid decline to infective arthritis that once was rampant in the days when tuberculosis, leprosy, typhoid, syphilis and other organisms lacked effective controls. Together with RA, other connective tissue disorders like systemic lupus erythematosus, progressive systemic sclerosis, dermatomyositis and others have been found to be on the increase in this country (Tay and Khoo, 1970 (a) and (b)).

Compared with other countries, the local incidence of RA is considerably smaller (Duthie *et al*, 1955, Lawrence 1963, Gilliland and Mannik, 1974). For instance the ratio of new RA cases to all new hospital admissions obtained from England (Sze, 1963), Japan (Schichikawa, 1966), Malaysia (Toh

et al, 1973) and Africa (Greenwood, 1969), showed that Singapore is intermediate between the temperate and the tropical countries (Table I (b)). Geographical factors are probably responsible for some of the observed differences. These could be environmental influence, genetic predisposition, social and cultural makeup and others. It is quite possible that climate plays an important role as it can certainly modify the RA symptoms. Warm weather often exerts a beneficial effect in preventing frequent relapses. However, a previous geographical study done by Lawrence and co-workers failed to show any relationship between RA incidence and the change of latitudes (Lawrence *et al*, 1966). The high Chinese percentage (70.5%) in this study did not imply the RA preponderance in this race. The percentage found corresponds closely to that of Chinese distribution in the local population. Similarly, in Malaysia, no significance preponderance was observed between the three ethnical groups—Chinese, Malays and Indians (Toh *et al*, 1973).

Female dominance in RA has been shown in all series except one from Nigeria (Greenwood, 1969). As in Western countries and in Japan, the local females outnumbered males by 2.4: 1 ratio (Duthie *et al*, 1955; Kersley 1962; Lawrence *et al*, 1966, Schichikawa, 1968). It has been known that occupations and social classes are not important in RA. This is true in our experience. The high incidence of housewives affected in this series was due to the larger number of adult females in the 21 to 60 age-groups. Once affected, the disease often becomes chronic with numerous remissions and relapses. In the males, young students and servicemen seemed to be the chief victims. The reasons for the sex difference have not been fully established.

The mean age of onset of RA varied from country to country. In England, it was 45 years and above (Sze, 1963). In Nigeria (Africa) it was between 21 to 40 years. Here in Singapore, the mean age for all females was 46.2 years and for males was 30.7 years, again, an intermediate value between the English and Nigeria series. This age difference was attributed to the mean age of the general population. In Singapore, more than half of our population are below the age of 20, while in countries like England and U.S. a much older populace than ours is found.

RA in the local series affects younger males who usually presented with acute symptoms of short duration (1.9 years) while the older females often had the subacute to chronic form of polyarthritides—from one to as long as twenty years (average 3.5 years). In the Nigerian series, the duration of RA for females and males were 1.6 and 1.8 years respectively (Greenwood, 1969). The shorter duration of RA in both the Nigerian and our series could account for the relatively benign course of the disease since the rheumatoid complications have not fully developed. The presence of positive family history confirms that RA not uncommonly occurs in family aggregations but whether this is due to a genetic predisposition or to environmental influ-

ences, remains to be explained. (Gilliland and Mannak, 1974).

Except for minor differences it is found that the pattern of joint involvement in this and other series is fairly uniform. The Nigerian pattern however, (Table IV) appears to be different. It has a much lower incidence of involvement of the fingers, wrists and knees but a higher incidence of ankle and cervical lesions. The difference might be due to the social habits or/and different environmental factors. Again, further explanation is needed.

In Singapore, the high incidence of knee joint involvement in RA patients often posed great hardship as these patients have great difficulties in climbing the stairs of the high-rise Housing Board Flats and in squatting in the toilet. The lesions of interphalangeal and metacarpophalangeal joints not only prevented them from working for their livelihood but also limited their daily activities.

Since hospital admission is generally not warranted in mild cases, the patients admitted to our department, had severe disease (Table IVb). The shortage of hospital beds demands that only the extremely ill cases were admitted and this pattern is shown in the hospital figures of Nigeria and Malaysia. Incidentally, we also had a higher incidence of patients with grade 3 activity as compared to the other hospital series as these cases were actually hospitalised for acute medical conditions unrelated to RA—our department being a general medical unit. Functional capacity of these patients was either markedly or moderately restricted (Table IVc). A lower incidence of grade IV functional incapacity (13.7%) in this series compared with other series suggests that the local patients have the more benign form of RA. As this incapacity was found to be of a transient nature, it was mainly due to soft tissue inflammation rather than to the severe and permanent crippling condition which followed bony deformities.

Extra-articular manifestations of RA were detected in 75% of Western—subjects (Gordon *et al*, 1973) but we have only 38% with these features. It is thought that these features correlate more with the severity of the disease process rather than with the disease duration or with the administration of drugs like corticosteroids. They often result in high morbidity and mortality and demand immediate medical attention.

The low frequency of positive Rheumatoid Arthritis factor (RAF) has been reported in Nigeria and Malaysia, the incidence being 9% and 19% respectively. In this series, 41% were seropositive. The low incidence of RA was not due to laboratory techniques but could be attributed to some factors in the serum of the patients of the tropics, modifying the RAF. African studies have shown that the difference was not due to genetic characteristics but probably to some environmental factors which affect the immunoglobulin levels. These include chronic infections like malaria, tuberculosis and infesta-

tions like parasitic intestinal worms (Greenwood *et al*, 1970). On the other hand, non-rheumatoid subjects in these tropical areas have been found to have positive RAF of 2 to 5% which was not detected in similar subjects of the temperate countries (Glynn, 1968; Lim and Leong, 1967). Cumulative effects of a variety of infections and infestations again were implicated (Wells, 1967). The precise explanation therefore must await further investigations.

Confirming the clinical picture, the radiological findings in the present series revealed a much lower incidence of erosive arthropathy. The majority had Grade 0 and Grade 1 changes according to Kellgren's criteria (1957). Severe radiological changes were mainly found in seropositive patients with prolonged rheumatoid activity of 5 to 20 years. They were those with partial or permanent functional disabilities. Fewer complications were encountered during the course of the diseases than expected. However, side-effects from chemotherapy were common. Bleeding from gastrointestinal tract, drug rash and recurrent bacterial infections were not infrequent and special precautions should be undertaken when administering drugs such as the salicylates and the indomethacin. Majority of our patients could tolerate moderate doses of salicylates, indomethacin and antacids in combination. Gold salts, penicillamine and cyclophosphamide were used rarely and only in the fulminating and rapidly progressive RA. None of our cases developed systemic amyloidosis, a condition frequently encountered in RA subjects of Western countries. On the other hand, Singapore has many cases of lichen amyloidosis, a primary cutaneous amyloidosis which is extremely rare in the West. These observed differences have not been adequately explained and need further studies.

The prognosis in the present series, on the whole, is comparatively more favourable than that observed in the temperate Western countries. Robinson (1963) observed that 35 to 50% of RA in temperate countries deteriorated into complete or partial incapacity by 10 to 15 years, whereas the local incidence was 13.1%. About a fifth in this series remained unchanged with frequent relapses and remissions and out of 10 patients that died in the 9-year study, only two were attributed to the RA process.

Thus although RA is comparatively benign locally than in the temperate countries, more than a third of the cases will continue to suffer from its intermittent or continued activity in spite of systemic chemotherapy.

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