Familial Tendency of Rheumatoid Arthritis among Patients Attending Specialist Clinics in Sri Lanka

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***Abstract*—** *Rheumatoid arthritis (RA) is an auto immune disease mainly caused by a combination of genetic and environmental factors. Few studies on familial incidence for RA have been conducted in Sri Lanka. The aims were to document patients with RA who have one or more family members affected with RA, describe special clinical features associated RA and determine the patterns of inheritance of familial RA. A descriptive and cross sectional study with 100 consecutive patients with confirmed diagnosis of RA attending specialist Rheumatology clinics were recruited. Data were collected using an interview administered questionnaire, relevant physical examination and testing for Rheumatoid Factor (RF). A complete three generation pedigree was complied for participants with positive family history. The data were entered and validated in a SPSS data base and some data was analysed using descriptive statistics. The statistical significance difference was analyzed using chi-square test. The vast majority of participants (92%) were females. Only 23% had positive family history. In 46%, the onset was before the age of 40 years and 16 out of 23 with positive family history manifested before 40 years. Forty one percent (41%) of the participants had positive RF, in which 10% (10/23) were in the familial group. The commonest clinical feature was arthritis of 3 or more joints (80%) and commonly involved joints were hands and wrists. Soft tissues surrounding the joints (35%) which were most common non articular manifestation, in which 9% was in the familial group. Out of patients with family history 17 had an autosomal dominant (AD) pattern of inheritance while 6 had AD pattern with reduced penetrance. The sporadic form of the disease was more common among study population. The age of onset of the disease was earlier among patients with positive family history. RF, clinical features, joint involvement and non- articular manifestation did not have any marked difference depending on the family history. AD pattern of inheritance was more common.*

***Keywords*—** *Rheumatoid Arthritis, Autosomal Dominant, Inheritance*

I. INTRODUCTION

Rheumatoid arthritis (RA) is chronic symmetrical poly arthritis of unexplained cause. RA is characterized by chronic inflammatory synovitis of mainly peripheral joints. It is typified by widespread persisting synovitis. Its cause is extremely variable but the production of rheumatic factors by plasma cells in the synovium and the local formation of immune complexes play a part. RA has a worldwide distribution. It affects 0.5-3% of the population. It is a significant cause of disability and mortality and carries a high socio-economic cost. RA presents from early childhood to late old age. The most common age of onset is between 30 and 50 years (Shipley *et al.,* 2005).

The possibility of infectious triggers, genetic predisposition, and autoimmune response are the factors associated with RA (Krishna, 2004). RA is a multifactorial disease caused by a combination of genetic and environmental factors. The genetic factors are involved in the pathogenesis of RA. Alleles of various genes are probably involved in the development of RA. HLA-DRB1 is the main RA gene, and it accounts for only part of the familial risk for RA. HLA-DRB1 alleles are neither necessary nor sufficient to cause the development of RA in a given individual. The populations from France, Japan, North America and UK have confirmed the role of the HLA region and suggested other susceptibility loci. Several genes implicated are TNFR2, PADI4, SLC22A4, RUNX1, and PTPN22 (Dieudé, and Cornélis. 2005).

The aim of this research was to study genetic predisposition of rheumatoid arthritis in patients with rheumatoid arthritis attending, the Rheumatology Clinics of the National Hospital of Sri Lanka (NHSL). Only few studies of genetic predisposition have been conducted in Sri Lankan patients with RA. Therefore, it would be useful to investigate further, whether Sri Lankan patients have any significant familial occurrence of RA. This information will be useful to understand the underlying causes for the disease and for counselling and managing affected individuals and their family members.

II. METHODOLOGY

The descriptive cross sectional study was conducted with 100 patients (diagnosis of RA) as study population in the setting of Rheumatology Clinics of the National Hospital Sri Lanka. The data were collected using an interview administered questionnaire, relevant physical examination and testing for Rheumatoid Factor (RF). A complete three generation pedigree was complied for participants with positive family history. The data were entered and validated in a SPSS data base and some data was analyzed using descriptive statistics. The statistical significance difference was analyzed using chi-square test. Ethical clearance was obtained from Ethics Review Committee, Faculty of Medicine, University of Colombo. Ethical issues were considered at all time by preserving confidentiality of the personal information of research participants.

III. RESULTS

The vast majority of participants were females (92%). So, in the study population the female to male ratio was 12:1. The patients with RA who had family history were 23%. Only 8% of patients of the total study population gave a history of consanguinity while 4 patients with genetic predisposition gave a history of consanguinity. It was difficult to identify a relationship of consanguinity and familial occurrence of the disease. Gender distribution of the study population is presented in Table 1.

Table 1: Gender distribution of the study population

Gender	**Distribution of the presence or absence of the affected family member**			
	Family history Yes		**Family history No**	
Male	01	4.3%	07	9.0%
Female	22	95.6%	70	90.9%

In 46%, the onset was before the age of 40 years and 16 out of 23 with positive family history manifested before 40 years. None of patients had developed the disease after the age of 60 in the familial group while this was 28.57% in the non-familial group. There was a relationship of age of onset with presence or absence of family history ($p<0.05$). The age of onset of study population with presence of absence of family history is presented in Table 2.

Table 2: The age of onset of study population with presence of absence of family history

Age of onset	**Distribution of the presence or absence of the affected family member**			
	Family history Yes		**Family history No**	
11-40 Years	16	34.8%	30	65.2%
41-60 Years	07	15.2%	39	84.8%
61-80 Years	00	0.0%	08	28.57%

The Relationship of rheumatoid factor with presence or absence of family history is presented in Table 3. Forty one percent (41%) of patients developed rheumatoid factor in the serum. From patients with rheumatoid factor, 10% (10/23) of patients had positive family history. No relationship was observed between rheumatoid factor and a presence or absence of the disease ($p>0.05$).

Table 3: Relationship of rheumatoid factor with presence or absence of family history

Diagnostic criteria	**Distribution of the presence or absence of the affected family member**			
	Family history Yes		**Family history No**	
Positive serum-yes	10	43.5%	31	40.3%
Positive serum-No	13	56.5%	46	59.7%
Total	23	23.0%	77	77.0%

The most common clinical feature observed was arthritis of 3 or more joints (80%). The positive family history showed higher percentage (82.6%) than the patients without family history (79.2%) of this feature. The commonest presenting feature was morning stiffness (45%). Rheumatoid subcutaneous nodules were the less presenting clinical feature in both familial and non familial group (21.7% and 11.6%). The presence of diagnostic criteria with the presence or absence of family history is presented in Table 4. Chi square test was used to identify the relationship between clinical features and familial occurrence of the disease. There was no relationship evident with any clinical feature and the presence or absence of family history ($p>0.05$).

The presence of joint involvement with presence or absence of family history is presented in Table 5. The commonly involved joints were hands and wrists (79%) irrespective of family history. This was 91.3% in familial group and 75.3% in non familial group. Chi square test was used to identify any relationship with joints

involvements and the presence or absence of family history. It was observed that there was no relationship between joints involvements and familial occurrence of the disease (p>0.05).

Table 4: The presence of diagnostic criteria with the presence or absence of family history

Diagnostic criteria	Distribution of the presence or absence of the affected family member				
	Family history Yes		Family history No		Total
MS	14	60.8%	31	40.3%	45%
SOW	08	34.7%	25	32.4%	33%
SJS	10	43.4%	34	44.2%	44%
HXC	07	30.4%	15	19.5%	22%
RSN	05	21.7%	09	11.6%	14%
RF	10	43.4%	31	40.3%	41%
AOJ	19	82.6%	61	79.2%	80%

- MS: Morning stiffness for at least 1 hour
- SOW: Swelling of wrist, MCP,PIP joints
- SJS: Symmetric joint swelling
- HXC: Hand x-ray changes typical of RA
- RSN: Rheumatoid subcutaneous nodules
- RF: Rheumatoid factor
- AOJ: Arthritis of 3 or more joints

Table 5: The Presence of joint involvement with presence or absence of family history.

Joints involvement	Distribution of the presence or absence of the affected family member				
	Family history Yes		Family history No		Total
Hand & wrist	21	91.3%	58	75.3%	79%
Elbows	11	47.8%	37	48.1%	48%
Shoulders	15	65.2%	46	59.7%	61%
Cervical	11	47.8%	34	44.2%	45%
Knees	21	91.3%	55	71.4%	76%
Ankles	16	69.5%	51	66.2%	66%
Feet	12	52.2%	23	29.8%	35%
Hips	08	34.8%	25	32.5%	33%
Others	04	17.4%	09	11.7%	13%

The presence of non articular manifestations with presence or absence of family history is presented in Table 6. The commonest non articular manifestation observed in the study population was soft tissue surrounding joints (35%). This was 39.1 % in familial and 33.8% in non familial group. Heart and peripheral vessels are considerable low number of patients affected in both familial (8.6%) and non familial group (5.2%). Vasculitis and Spleen & lumph nodes are not present in the study population.

Table 6: The presence of non articular manifestations with presence or absence of family history

Diagnostic criteria	Distribution of the presence or absence of the affected family member				
	Family history Yes		Family history No		Total
Soft tissues Surrounding joints	09	39.1%	26	33.8%	35%
Heart & peripheral vessels	02	8.60%	04	5.20%	06%
Vasculitis	00	0.00%	00	0.00%	00%
Lungs	00	0.00%	05	6.50%	05%
Spleen & Lymph	00	0.00%	00	0.00%	00%

Table 7 shows the pattern of inheritance of the patients those with a family history. Out of patients with family history 17 had an autosomal dominant (AD) pattern of inheritance while 6 had shown AD pattern with reduced penetrance.

Table 7: Pattern of inheritance of the patients those with a family history

Pattern of inheritance	Number of patients	Percentage (%)
Autosomal Dominant	23	100.0%
Autosomal Recessive	0	0.0%

IV. DISCUSSION

The results of the present study show that rheumatoid arthritis was more common among females than in males irrespective of family history with a ratio of 12:1. This finding was on agreement with a previous study done by Balsa, *et al.,* (2000).

Only 23 of patients showed, at least one affected member in the family. This indicates that there is a familial occurrence of the disease. However, a large portion of the population (77) the disease occurred sporadically. This finding is similar to the study done by Hasstedt, et al., (1994) who showed that a large portion of RA cases occur sporadically though genes may account for the remaining familial RA. Shipley, et al., (2005) expressed that RA is familial but sporadic and it affects several generation. Further, Laivoranta-Nyman, et al., (2003) also stated that the familial RA patients showed

frequencies of HLA-DR4 as compared with non-familial RA group. However, it was difficult to identify whether there was a relationship between gender distribution and the presence or absence of family history in this study because of the small sample size.

It was observed that there was a relationship of age of onset and familial occurrence of the disease ($p<0.05$). The age of onset of the disease was lower among patients with family history while patients without family history had a later age of onset of the disease. This finding is similar to the study of Taneja V. et al, (1993) who recorded that the mean age of onset of RA was significantly lower in the familial than in the sporadic RA patients.

There was no relationship evident between clinical features and familiarity of the disease. These findings were in agreement with the study reported by Sanders, (1997) who stated that there is a similarity of clinical features in familial and sporadic RA groups. Moreover, Balsa, et al., (2000) also had shown that clinical characteristics of familiar RA in Spain do not seem to be different from sporadic RA.

In the present study, no significant relationship between positive RF in serum and the presence of the family history ($p>0.05$) was identified. These findings demonstrate that, irrespective of family history any patient can develop serum rheumatoid factor. These results were similar to what was reported Sanders, et al., (1997) who demonstrated that seropositive for rheumatoid arthritis was similar in familial and sporadic form of the disease while Silman A, (1988) also has stated that the existence of genetic heterogeneity will not affect for the development of the RF.

According to the present study, there is a familial occurrence of the disease which accounts for a 23% of the study population. 17 patients with family history showed an autosomal dominant (AD) pattern of inheritance while 6 had shown autosomal dominant inheritance with reduced penetrance. There were no patients with an autosomal recessive pattern of inheritance. But, in contrast, a study of Rigby, (1991) has stated that familial RA was close to recessive expectations while the dominant mode of inheritance was rejected. In AD inheritance pattern, mother transmits the disease while father does not. Therefore, there is a high possibility that the disease has a maternal transmission and there is a reduced penetrance of the disease in males. These findings are similar to Koumantaki, (1997) who suggested that mothers confer RA on their offspring more often than fathers.

V. CONCLUSION

According to the findings of the present study, RA is about twelve times commoner among females than males. Females develop the disease much earlier than males irrespective of the family history. This study demonstrates that sporadic form of the disease is much more common than the familial form. The age of onset of the disease is earlier among patients with family history than those with no family history. Involvements of joints, non-articular manifestation do not have any marked difference depending on the presence or absence of family history. The commonest pattern of inheritance is autosomal dominant among the familial form while there was no evidence of autosomal recessive pattern of inheritance.

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