Impact of opportunistic factors on Rheumatoid arthritis

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Abstract- **Rheumatoid Arthritis (RA) is an auto-immune diseasein which body mistakenly considers some parts of its own system as pathogens and attacks them. Prevalence of approximately 0.75% in India. About 40% diseased become work disabled within 5 years from onset of symptoms. The objectives of this paper are to correlate incidence rate and the associated sign/ symptoms of clinically suspected patients. The study is based on 290 clinically suspected subjects. Cross-sectional cohort study design was used. Clinically suspected cases were referred by different OPD's of Sir Sunderlal Hospital for screening. Along with results of these tests other socio-demographic, economic information were also carried through structured pre-tested schedule method Study concluded that the differences observed among the various blood tests and positivity rate was found statistically highly significant. Although the study found substantiation of maximum percentages of RA patients having knee difficulty besides related studies in Indian context. Detection of AntiCCP is thoroughly practicable for the diagnosis of RA, in fact even RF likewise quite valuable for diagnosis of RA and combination of testing for both RF and AntiCCP may be even more useful in comparison to individual test**.

Keywords **- Rheumatoid Arthritis, Demographic, sign/ symptoms, Cross-sectional**

INTRODUCTION

In AIHW (2009) defines RA is an inflammatory, autoimmune disease that causes pain, joint stiffness—especially in the morning and loss of function. Although there are many forms of arthritis, of those commonly known, rheumatoid arthritis is the most serious and the second most common (after osteoarthritis). It can occur at any age but is more common in persons over the age of 30 years and affects women more often than men. The disease generally presents in a symmetrical (both sides of the body) pattern, most often involving the hand joints. RA affects the whole body, including several organs, and so is described as a systemic disease.[1] Progressive and irreversible joint damage is caused by the immune system attacking its own body tissues, particularly those lining the joints. Joint pain and swelling lead to structural deformities and disability, causing a reduction in joint movement and muscle use. In turn, muscle size and strength decreases and the resulting abnormal forces on tendons cause deformity. The disease can also lead to problems with the heart, respiratory system, nerves and eyes. The underlying cause of the disease is not well understood. RA strikes people in different ways. In some cases, the disease starts suddenly over several days to weeks. For the remainder, it starts more gradually over a period of several weeks to months. In a small proportion (5%), the disease will disappear after 4 to 8 weeks. For another 10% of cases there may be periods of improvement which can last up to several years. In the majority of cases however, it becomes chronic. There may be periods of comparative remission, where symptoms decrease markedly, but in the longer term without effective treatment the disease causes much damage and disability. [2]

According to Feinstein and Brent (2006) presence of morning stiffness is key of articular feature. Morning stiffness can be defined as "slowness or difficulty moving the joints when getting out of bed or after staying in one position too long, which involves both sides of the body and gets better with movement."[3] Most patients with RA report some degree of morning stiffness. However, morning stiffness, by itself, may not be a good discriminator between the different arthritic conditions. RA is the number one cause of early retirement from service. [4] The social and economic consequences for the individual are drastic even in the first year after onset of disease, Within seven years, up to 40 percent of patients are no longer able to work in their profession.[5] According to WHO (2003), this percentage rises significantly as RA progresses: ten years after onset of the disease, nearly 60 percent of RA patients are no longer able to

work. [6]

MATERIAL AND METHODS

Study population

The present study is based on prospective cross-sectional cohort study design. In the present study 290 (110 male and 180 female) clinically suspected of rheumatoid arthritis patient were studied. Who were screened at UGC Advanced Immunodiagnostic Training and Research Centre, Department of Pathology, IMS, BHU, Varanasi, U.P. The cases were referred by different OPD's of Sir Sunderlal Hospital. Mostly screened subjects were from eastern Uttar Pradesh, western Bihar, Madhya Pradesh and Jharkhand. About 2-ml of blood samples were collected in plain vial from each patient and each sample were tested by the laboratory person.

Study design

ACR/EULAR 2010 criteria were evaluated at baseline. The baseline assessment included a standardized interview, general physical examination, and standardized rheumatologic evaluation, including the number of swollen and tender joints, the distribution and symmetry of synovitis, the size of involved joints, and the presence of rheumatoid nodules. Laboratory investigations included acute-phase reactants and rheumatoid factor assays.

The ACR/EULAR criteria were considered positive in patients with no other diagnosis explaining the symptoms and with either erosions typical for RA or a score greater or equal to 6/10:

- joint involvement (1 medium-large joint: 0 points; 2 to 10 medium-large joints: 1 point; 1 to 3 small joints: 2 points; 4 to 10 small joints: 3 points; 10 joints with at least one small joint: 5 points);
- serology (no rheumatoid factor [RF] or ACPA: 0 point; low- positive RF and/or ACPA [less than 3 times the upper limit of normal for the laboratory and assay]: 1 point; high positive RF and/or ACPA [more than 3 times the upper limit of normal for the laboratory and assay]: 3 points);
- synovitis duration (less than 6 weeks: 0 point; greater or equal to 6 weeks: 1 point) and acute-phase reactants (Creactive protein [CRP] and erythrocyte sedimentation rate [ESR] normal: 0 point; CRP and/or ESR elevated: 1 point).[7]

STATISTICAL ANALYSIS

The responses received through the interview schedule were coded, grouped, processed and tabulated. Data were entered into MS-Excel spreadsheet and were analyzed by using SPSS package (16.0 Version) by importing the Excel spreadsheet into SPSS 16.0. All items of the various criteria set at baseline. Data has been presented in number and percentage. 2010 ACR/EULAR criteria use to determine which baseline features to separated patients with and without RA.

RESULTS

Signs and symptoms profile of the study subjects

While early signs and symptoms of RA can be mimicked by other diseases, the symptoms and signs are very characteristic of rheumatoid disease. Early RA tends to affect smaller joints first — particularly the joints that attach fingers to hands and toes to feet.

RA signs and symptoms may vary in severity and may even come and go. Periods of increased disease activity, called flares, alternate with periods of relative remission — when the swelling and pain fade or disappear. Over time, RA can cause joints to deform and shift out of place.

TABLE1: Distribution of Signs and symptoms profile of the study subjects

Sign/Symptom	Number	Percentage (%)
Fever	57	19.7
Dizziness	26	8.9
Tiredness	72	24.8
Joint Pain	66	22.8
Joint Swelling	57	19.7
Ankle Swelling	5	1.7
Back Pain	46	15.9
Muscle Pain	18	6.2
Neck Pain	18	6.2

Table1 Illustrates the distribution of study subjects by their health related issues like signs and symptoms at the time of data collection. In the figure data clearly depicts that most of the study subjects was suffering from tiredness. After that joint pain shows leading problem in RA as compare to other signs and symptoms i.e., 22.8% . Followed by fever and joint swelling possess identical percentage (19.6%) . Relatively much majority of study subjects was showing back pain (15.9%).

In the diagram 6.2% of the study subjects displays the muscle pain as well as neck pain. Approximately nine percent of study subjects was suffering from Dizziness. Thus, it observed from finding that those respondents who have the ankle swelling (1.7%) had occupied lowest position in the figure.

Joints involvement of the study subjects

Arthritis refers the more than 100 condition that affects the musculoskeletal system, specially the joints. The joints are the part of the body where bones connect. When arthritis is present, the joints may become inflamed, stiff. red and painful.

RA is the one type of arthritis classified as systematic meaning it affects the entire body. Damage from RA may occur in tissues surrounding the joints including the tendons, ligaments and muscles.

Likewise in this study most of the common areas of the body were included.

TABLE 2: Distribution of Joints involvement of the study subjects

Involved Joints	Number	Percentage
Finger	75	25.9
Wrist	60	20.7
Toes	18	6.2
Shoulder	53	18.3
Neck	35	12.1
Back	82	28.3
Elbow	18	6.2
Ankle	43	14.8
Knee	179	61.7
Hips	51	17.6

In the present study majority of the study subjects suffering from knee problem i.e., 61.7% It is far-flung from other variables in joints involvement. After that a quantity of leading portion of the study subjects belongs to criteria back (28.3%) and finger (25.9%) joints respectively. In the figure wrist exhibits also higher occurrence (20.7%) in present study. In the figure clearly shows that approximately similar percentage of study subjects suffered by shoulder (18.3%) and hips(17.6%) joints respectively. Approximately fifteenth percent of study subjects were having pain in ankle. Overall, 12.1% subjects suffering from neck problem which is at second last place in the above figure. In the figure clearly displays that two variables toes and elbow occupy last place .i.e., 6.2%.

Difficulties in daily activity of the study subjects

There are 5 sections: dressing, arising, eating, walking, and taking help from other persons. There are 2 or 4 questions for each section. Scoring within each section is from 0 (without any difficulty) to 3 (unable to do). For each section the score given to that section is the worst score within the section, i.e. if one question is scored 1 and another 2, then the score for the section is 2.

TABLE 3: Distribution of study subjects by difficulties in daily activities

Daily Activities	no difficulty	some difficulty	Muchdifficulty	Unable to do
Difficulties in dressing and grooming				
Shoelaces& Buttons	204(70.3)	79(27.2)	6(2.2)	1(0.3)
Shampoo/Oiling hair	205(70.7)	78(26.9)	6(2.1)	1(0.3)
Difficulties in Arising				
Stand up from a straight chair	106(36.6)	102(35.2)	77(26.6)	5(1.6)
Get in and out of bed	105(36.3)	103(35.5)	77(26.6)	5(1.6)
Difficulties in Eating.				
Cut your vegetable/meat	214(73.8)	69(23.8)	5(1.7)	2(0.7)
Lift a full glass to your mouth	217(74.8)	66(22.8)	5(1.7)	2(0.7)
Difficulties in Walking.				
Walk outdoor on flat ground	157(54.1)	91(31.4)	38(13.1)	4(1.4)
Climb 5 steps up	90(31.0)	121(41.7)	73(25.2)	6(2.1)
Go down 5 steps	90(31.0)	121(41.7)	73(25.2)	6(2.1)
Walk on uneven ground	126(43.4)	107(36.9)	53(18.3)	4(1.4)
Need help from another person for				
Dressing & Grooming	272(93.8)	15(5.2)	3(1.0)	0(0.0)
Arising	273(94.1)	15(5.2)	2(0.7)	0(0.0)
Eating	280(96.6)	8(2.7)	2(0.7)	0(0.0)
Walking	259(89.3)	26(9.0)	5(1.7)	0(0.0)

Table 3 depicts the distribution of study subjects by difficulties in daily life activity. Measurement of functional disability was done in all subjects at the time of data collection. In the present study approximately 70% were considered in no difficulty under dressing/grooming like put shoeless/buttons of his/her shoes/shirt and similar percentage of subjects shows no difficulty in shampoo/oiling hair. Only 0.3% subject had unable to do it. Now if considered no difficulties in arising like stand up from straight chair and go in & out of bed, about both had similar percentage (36%). After that table shows that 26.6% of subjects having much difficulty. Not more than 1.7% of subjects show that they were unable to do it. Whereas difficulties in eating associated effort shows 73.8% of study subjects having no any difficulty in cutting vegetables/meat and 23.8% having some difficulty, while 0.7% were unable to do

it. 217(74.8%) were showing no any difficulty in lifting a full glass to his/her mouth although 66(22.8%) were showing some difficulty, while 0.7% were not capable to do it. Difficulties in walking are divided in four different criteria i.e., walk outdoor on flat ground, climb 5 step up, go down 5 step , walk on uneven ground. In which majority of study subjects had no difficulty in walk outdoor on flat ground (54.1%). Followed by walk on uneven ground (43.4%) , climb 5 step up (31%) and go down 5 step (31%) respectively. In climbing 5 step up or down, (41.7%) in both were showing some difficulties. In that order 107(36.9%) and 91(31.4%) had some difficulty in walk on flat or uneven ground. overall, only 2.1% of study subjects were unable to climb up or down 5 step. In the last section of daily activity approximately 90% to 96% of the study subjects were not taking help from another person for dressing & grooming, arising, eating and walking.

Investigation profile of the study subjects

RF (RF are not very specific for this disease and can also be detected in other rheumatic disorders, infections, and in apparently healthy individuals), AntiCCP (Anti-CCP is present in patients, before symptoms develop) & acute phase reactant CRP (CRP is classified as an acute phase reactant, which means that its levels will rise in response to inflammation) test and himself reported for sample collection.

TABLE 4: Distribution of study subjects by blood test result

Blood test	Number	Percentage
RF	61	21.0
AntiCCP	62	21.4
CRP	94	32.4
CRP or AntiCCP	112	38.6
CRP and AntiCCP	39	13.4
RF or AntiCCP	95	32.8
RF and AntiCCP	27	9.3
RF or CRP	106	36.5
RF and CRP	46	15.9
RF or AntiCCP or CRP	128	44.1
RF and AntiCCP and CRP	26	8.9

Sixty two out of 290 samples tested positive for anti-CCP. This compared with 61/ 290 samples tested positive for RF and acute phase reactant shows 94 samples tested positive which is highest number of samples among them for CRP. Table shows that our experience with the serological tests anti-CCP, RF, CRP and the combination of , (CRP and AntiCCP), (RF and AntiCCP), (RF and CRP) and (RF and AntiCCP and CRP) of 290 clinically suspected RA patients , Percentage of RF is 21.0%, percentage of anti-CCP is 21.4%, percentage of CRP was 32.4%, In combination of serology test majority of study subjects belongs to group (RF or AntiCCP or CRP) in comparison to only 9.7% belongs to combination of (RF and AntiCCP and CRP). Whereas in combination of (CRP or AntiCCP) shows 39.3% and (CRP and AntiCCP) had only 16.2%. Followed by group (RF or CRP) present in study subjects were 38.3% and group (RF and CRP) had 16.2%. Further, in figure combination of (RF or AntiCCP) represents 32.4% of total study subjects. Whereas (RF and AntiCCP) shows minimum percentage i.e., 9.7%.

DISCUSSION

Presence of opportunistic infections (Signs & Symptoms)

According to arthritis foundation Atlanta, along with pain, many people experience fatigue, loss of appetite and a low-grade fever. The symptoms and effects of RA may come and go. A period of high disease activity (increases in inflammation and other symptoms) is called a flare. A flare can last for days or months. Ongoing high levels of inflammation can cause problems throughout the body.[8] In addition to present study distribution of positivity rate among the study subjects according to their signs and symptoms present in them and referred by consultants during their visit to the place of study. The significant morbidities with RA were fever, Dizziness, Tiredness, Joint pain, Joint swelling, Ankle swelling, Back pain, Muscle pain and Neck pain. Generally, signs and symptoms of RA begin insidiously and are additive over weeks to months. They commonly include fatigue, malaise, generalized stiffness, and generalized arthralgias or myalgias. Synovitis usually develops gradually, often involving the hands, wrists, knees, or feet, often symmetrically. However, in 10% to15% of patients, the onset of disease is explosive, with polyarthritis, fever, lymphadenopathy, and splenomegaly developing over days to weeks.[9],[10] The positivity rate was 29.8% among the suspects suffering from fever and 13.3% among those not suffering with fever. Positivity rate was approximately 4 times higher in suspects suffering from dizziness than those who were not having dizziness Positivity rate was more than double in subjects suffering from tiredness than those not having 31.8% positivity was observed in suspects suffering from joint pain, 12.1% in those not having joint pain. Assessments in RA mainly look at joint inflammation.[11] Moreover in present study joint swelling, ankle swelling and neck pain positivity rate where approximately more than 2 times higher in suspects suffering from these

signs and symptoms than those who were not suffering from these signs and symptoms. Out of total RA patient only 8.3% RA patient were having ankle swelling. The differences among them were statistically highly significant. 11.1% positivity was observed in suspects suffering from muscle pain, 16.9% in those not having muscle pain. The differences among them were statistically not significant.

Joints involvement of the study subjects

RA is a chronic inflammatory disease characterized by joint swelling, joint tenderness, and destruction of synovial joints, leading to severe disability and premature mortality. [12]-[15] The significant body ache with RA were Finger, Wrist, Toes, Shoulders, Neck, Back, Elbow, Ankle, Knee and Hips. Present study positivity rate was 41.3% among the suspects suffering from finger pain and 7.9%% among those not suffering with finger pain.

According to Dr. Friederike Hammar (2010) RA usually begins subtly, with swelling, pain, and problems with movement of the small and middle finger joints, as well as with unspecific symptoms like rapid fatigue and general weakness. If the disease is not stopped it leads to complete destruction of the joints. With periodicflare-ups, the disease marches inexorably onward, affecting more and more joints.[16]
National Institute for Health and Care Excellence (NICE, 2009) usually starts as an insidious symmetrical polyarthritis, often with nonspecific systemic symptoms. RA can affect any synovial joint but typically affects the small joints of the hands and the feet. It is usually bilateral and symmetrical in distribution. More joints are affected with progression of the disease.[17]

Positivity rate was approximately more than 2 times higher in suspects suffering from wrist involvement than those who were not having problem in wrist. Positivity rate was approximately one-fourth in subjects suffering from toes pain than those not having any difficulties in toes , 30.2% positivity was observed in suspects suffering from shoulder involvement , 13.5%% in those not suffering from shoulder problem.

Positivity rate in involvement of neck and back where approximately more than 2 times higher in suspects suffering from neck and back problem than those who were not suffering from neck and back problem.

Out of total RA patient only 16.7% RA patient were having difficulty in elbow. 39.5% positivity was observed in suspects suffering from ankle problem,16.9% in those not having ankle problem. Maximum percentages of RA patients having knee difficulty i.e., 83.3%. Out of total hips affected subjects 43.1% were RA patients. The differences among them were statistically highly significant ($P < 0.001$). In Indian context, reason behind majority in knee difficulties was reported by Kumar et al. (2002) that sitting cross-legged on the floor is a standard practice in India. Even the higher socio-economic strata of the society practice it in social or religious assemblies. This posture requires acute flexion of the knees besides abduction, flexion and external rotation of the hip joints. A similar set of joint movements is needed for another important activity in the Indian population, i.e. squatting in the toilet. Inability to perform either of these two activities means a major functional disability.

Difficulties in daily activity of the study subjects

According to Harris, cited in Dellhag and Burckhardt (1995), over ninety percent of people with RA are believed to have some involvement of their hand joints. This involvement often leads to diminished grip strength and difficulty with performing everyday tasks.[18]

The Health Assessment Questionnaire-Disability Index (HAQ-DI) was originally published in 1980 by Fries et al. from Stanford University, USA.[19] Three years later, Pincus et al. published an abridged version ('Modified HAQ' or MHAQ), retaining only eight questions out of the original 20 and showed that MHAQ captured the same information as obtained with the somewhat lengthy original questionnaire. [20] Pincus et al. recently published a more comprehensive instrument called the multi-dimensional HAQ (MDHAQ) in which advanced activities of daily living and items related to psychological domain were added to the MHAQ.[21] In present study measurement of functional disability was done in all subjects at the time of data collection. In the present study approximately 70% were considered in no difficulty under dressing/grooming like put shoeless/buttons of his/her shoes/shirt and similar percentage of subjects shows no difficulty in shampoo/oiling hair. Only 0.3% subject had unable to do it. Now if considered no difficulties in arising like stand up from straight chair and go in & out of bed, about both had similar percentage (36%). Further, 26.6% of subjects having much difficulty. Whereas difficulties in eating associated effort shows 73.8% of study subjects having no any difficulty in cutting vegetables/meat and 23.8% having some difficulty, while 0.7% were unable to do it. 217(74.8%) were showing no any difficulty in lifting a full glass to his/her mouth although

66(22.8%) were showing some difficulty, while 0.7% were not capable to do it. Difficulties in walking are divided in four different criteria i.e., walk outdoor on flat ground, climb 5 step up, go down 5 step , walk on uneven ground. In which majority of study subjects had no difficulty in walk outdoor on flat ground (54.1%). Followed by walk on uneven ground (43.4%), climb 5 steps up (31%) and go down 5 steps (31%) respectively. In climbing 5 step up or down, (41.7%) in both were showing some difficulties. In that order 107(36.9%) and 91(31.4%) had some difficulty in walk on flat or uneven ground. overall, only 2.1% of study subjects were unable to climb up or down 5 steps. In the last section of daily activity approximately 90% to 96% of the study subjects were not taking help from another person for dressing & grooming, arising, eating and walking.

Investigation profile of the study subjects

The presence of "rheumatoid factor" (RF) was identified in patients with RA over 50 years ago (Rose et al. 1949);[22] assays for RF remain one of the American College of Rheumatology (ACR) classification criteria for RA. 61(21.0%) out of 290 subjects found positive for RF, and out of 61 subjects, 37 had RA. This compared with 62 / 290 (21.4%) subjects found positive for anti-CCP. In which 36 had RA. Besides, over the past few years, many studies have evaluated the diagnostic performance of anti-CCP on a variety of diagnostic platform. [23]-[27]

High levels of C-reactive protein (CRP) are also indicators of active inflammation. Like the ESR, a high result does not indicate what part of the body is inflamed, or what is causing the inflammation.[28] Whereas in present study 94(32.4%) out of 290 subjects observed positive for acute phase reactant CRP and 93.8% positivity of RA out of total RA patients. The differences observed among the various blood tests and positivity rate was found statistically highly significant ($p<0.001$). If considered combinations of serology tests and acute phase reactant CRP or

AntiCCP, CRP and AntiCCP, RF or AntiCCP, RF and AntiCCP, RF or CRP, RF and CRP, RF or AntiCCP or CRP and RF and AntiCCP and CRP . It was observed that RF and AntiCCP and CRP showed minimum percentage of RA patients from total RA patients. whereas RF or AntiCCP & RF or AntiCCP or CRP both the combination had 100% outcome. The differences observed among the combination of various blood tests and positivity rate was found statistically highly significant ($p<0.001$). Detection of anti-CCP is very useful for the diagnosis of RA, in fact even RF also very useful for diagnosis of RA and combination of testing for both RF and anti-CCP may be even more useful in comparison to individual test. Early treatment of RA is important as it can prevent irreversible damage of the joints. Despite the strong diagnostic value of anti-CCP and RF, there is strong demand for novel serological biomarkers to further improve the early diagnostic of this abundant disease.[29]

CONCLUSIONS

Study concluded that the differences observed among the various blood tests and positivity rate was found statistically highly significant. Although the study found substantiation of maximum percentages of RA patients having knee difficulty besides related studies in Indian context. Detection of AntiCCP is thoroughly practicable for the diagnosis of RA, in fact even RF likewise quite valuable for diagnosis of RA and combination of testing for both RF and AntiCCP may be even more useful in comparison to individual test.

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