ORIGINAL ARTICLE

ASSESSMENT OF REQUEST PATTERN AND UTILITY OF RHEUMATOID FACTOR IN A TERTIARY HOSPITAL IN NORTH EAST NIGERIA

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ABSTRACT

Background: The diagnostic utility of Rheumatoid Factor (RF) test is not well documented. The question therefore is: - 'when is it appropriate to make this request'?When patients' own immunological defense mechanisms go awry and start attacking one's tissues, (autoimmune), there usually arises a problem. This usually affects the heart, musculo skeletal system and other organs giving rise to signs and symptoms that are seen in other ailments. The joints are the most common site of affectation and an early diagnosis may go a long way in managing the disease. Usually an antibody (Rheumatoid factor) is found in such patients. It is formed against the Fc portion of IgG, forming an IgG-Fc immune complex that normally leads to the disease process. It is this complex (usually an IgM) in the patient's serum that is exposed to a commercial antigen in the laboratory and the titer determined against a standard. The normal level is usually <14IU/ml. Levels higher are usually considered abnormally high, elevated or positive. A negative RF test however does not mean that the patient hasn't got the disease. Objective: To determine the frequency of positivity of rheumatoid factor and the context in which the requests are made by group of physicians and advise on when to make the request. Methods: A retrospective study of case notes of 354 patients requested to perform rheumatoid factor test at the immunology department over a period of 6 years were reviewed. The requesting departments, clinical and demographic characteristics of patients were reviewed and analyzed. Data analyzed using SPSS version 22. Results: Of the 354 requests made,265 (74.9%) were due to musculo skeletal symptoms and but20 (5.6%) were positive for RF. Of the 20, 19 (95%) had polyarthritis while 1 (5%) was asymptomatic. The mean age was 37.06±13.91 and 205 (57.9%) were females. Most (137 or 38.7%) of requests for RF were from the general out-patient department and 108 (30.5%) from medical out-patient department. The sensitivity and specificity for RF test in detecting MSK disease were 7.17% (95%CI, 4.37-10.97) and 98.88% (95%CI 93.90%, 99.97%). The positive likely hood ratio was 6.38% (95% CI 0.87, 40.99). The positive predictive value (PPV) and negative predictive value (NPV) were 95.0% (95%CI 77.02, 99.29%) and26.35% (95%CI 25.48, 35.30%). Test accuracy was 30.23% (95% CI25.48, 35.30%). Conclusion: We recommend that rheumatoid factor should be requested only in patients with fleeting arthritis,good clinical evaluation for signs and symptomsand looking for differentials.

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Key words: Rheumatoid disease, Rheumatoid factor, Polyarthritis, Paucity of positive results.

INTRODUCTION

Rheumatoid factors (RF) are auto antibodies first detected over 70 years ago and are found in a variety of both rheumatic and non-rheumatic diseases.[1, 2]The clinical utility of RF in detecting rheumatoid arthritis and other rheumatic disease is not an absolute diagnostic tool; however, its role in prognosticating patients with rheumatoid arthritis is well established.[3]

Rheumatoid factor (RF) test is a frequently requested test by General Physicians.[4, 5] A Spanishpopulation-based cohort report indicated that 10% of the request were made in patients without preexisting rheumatic or musculoskeletal diseases, about 22% of those tested were positive and only 2.6% of those positive cases developed Rheumatoid arthritis within one year.[4] Other reasons for requesting RF test as described by Sinclair and Hull *et al*[5] were low back pain (25%) and muscle pain (27%), however, in their study, most physicians requested for RF test in the context of polyarthritis, symmetrical arthritis and joint stiffness.

The prevalence of positive RF in the general population is between 0.18% and 4.3%[1, 6] and 60 -70% in patients with rheumatoid arthritis[7]. Variation in the prevalence is due to factors such as age, sex, smoking status and type of test used to detect RF.[1, 6]In a meta-analysis by Nishimura *et al*[8], the pooled sensitivity for RF was 0.69 (confidence interval (CI), 0.65–0.73) and specificity was 0.85 (CI, 0.82–0.88) in detecting rheumatoid arthritis. The specificity, sensitivity and diagnostic accuracy is however, low in detecting other rheumatic and non-rheumatic diseases.[9, 10]In addition, testing for RF inappropriately, incurs a substantial amount of economic cost on the patients and health care system.[9, 10]

This study is to determine the frequency of positive RF test, the physician sub-specialties who requested for RF, the clinical context leading to the RF request the test and the diagnostic accuracy of RF test in a tertiary health centre in North-East of Nigeria.

MATERIALS AND METHODS

We reviewed, collated and analyzed all requests for rheumatoid factor in the immunology department of University of Maiduguri Teaching Hospital (UMTH) from the 1st of January, 2005 to 31stDecember, 2010 (6 years). The study was approved by the ethics committee of UMTH. Three hundred and sixty-five (365) request were made but the clinical details of 11patients could not be traced and were excluded leaving patients 354 were that included in the study. Rheumatoid factor was tested using slide Latex Enhanced Immunoturbimetric technique, (Randox Reagents, UK).

Demographic variables extracted were age and sex. The referring clinicians were identified and categorized as physicians from General out-patient (GOPD), Medical out-patients (MOPD), Surgical out-patient (SOPD), Orthopaedics outpatients, Paediatrics, Gynaecology and others (patients referred from outside the hospital). Request from the respective specialty wards were classified as MOPD for medical wards or SOPD from surgical wards etc. Thetentative diagnosis of the referring physician were documented Vis a Visthe RF result. Diagnosis were categorized into musculoskeletal (MSK) and non- musculoskeletal (non-MSK) diseases or disorders.

Data obtained was analyzed using statistical package for social sciences (SPSS) version 22, (IBM USA).

Demographic and clinical data were summarized using frequencies, percentages and proportions. Test of normality was performed using Shapiro–Wilk statistics. Means of the ages were compared using T-test. Tests of association between RF test outcome and each of the determinants under consideration (age, sex, presence or absence of MSK condition, site of request and year of request) were done using Chi-Square Test; Fishers exact was used where frequencies are less than 5. Diagnostic statistics using cross tabulations was used to determine the likely hood ratio, sensitivity, specificity, positive Predictive and negative predictive value of the test with MSK disease as the definitive outcome.

MSK- Musculoskeletal, n=number, RF-rheumatoid factor, +ve – positive, -ve – negative, CI – Confidence interval, LR-likely hood ratio, PPV -positive predictive value, NPV- negative predictive value.

RESULTS

Three hundred and fifty-four (354) rheumatoid factor (RF) tests were requested over a period of 6 years (2005 to 2010). The highest frequency in a year were 82 (23.2%) in 2006.One hundred and thirty-seven (38.7%) requests were from the GOPD, 108 (30.5%) from the MOPD, 30 (8.5%) from the Orthopedic department and the remaining 79 (22.3%) were from departments of Paediatrics, Surgery, Gynaecology and referrals from other centres (table 1).

Demographic and clinical characteristics of the study population

The mean age of all patients was 37.06 ±13.91. They comprised of 205 (57.9%) females and 149 (42.1%) males. There was no significant difference between the ages of males and females (p=0.086). The most common reasons for RF test request were joint pains (n=233, 65.8%) and non-specific complaints like malaise and generalized body pains (n=60, 16.9%). Table 1 shows the other conditions in which RF test were requested.

Table 1: Demographic characteristics, year, clinical reasons and point of Rheumatoid Factor test request.

Characteristic	N=354 (%)
Age (mean)	37.06 ±13.91
Sex	
Male	149 (42.1)
Female	205 (57.9)
Year of request	
2005	50 (14.1)
2006	82 (23.2)
2007	61 (17.2)
2008	24 (6.8)
2009	61 (17.2)
2010	76 (21.5)
Point of Request	
GOPD	137 (38.7)
MOPD	108 (30.5)
SOPD	5 (1.4)
Orthopaedic clinic	30 (8.5)
Paediatric clinic	15 (4.2)
Gynaecology	3 (0.8)
Other sites	56 (15.8)
Diagnosis	
Polyarthritis	233 (65.8)
LBP	24 (6.8)
Fever with arthralgia	20 (5.6)
Routine screening	7 (2.0)
Suspected CTD	5 (1.4)
Knee pain	2 (0.6)
JIA	2 (0.6)
Visual disturbance	1 (0.3)
Others	60 (16.9)

N= number, %-percentage, GOPD- general outpatient department, MOPD-medical outpatient department, SOPD-surgical outpatient department, LBP- low back pain, CTD-connective tissue disease, JIA-juvenile idiopathic arthritis

Table 2: Distribution of positive and negative rheumatoid factor test according gender, age, site and year of request and the presence or absence of musculoskeletal complaints.

Characteristic	RF pos n=20(5.6%)	RF neg n=334 (94.4%)	P-value (chi square)
Sex			
Male	6 (4.0)	143 (96.0)	0.352
Female	14 (6.8)	191 (93.2)	
Age			
1-10	0 (0.0)	13 (100.0)	0.330
11-20	0 (0.0)	34 (100.0)	
21-30	4 (7.0)	53 (93.0)	
31-40	8 (5.2)	147 (94.8)	
41-50	4 (8.0)	46 (92.0)	
51-60	1 (4.2)	23 (96.8)	
61-70	2 (13.3)	13 (86.7)	
>70	1 (16.7)	5 (83.3)	
Clinics			
GOPD	8 (5.8)	129 (94.2)	0.400
MOPD	6 (5.6)	102 (94.4)	
SOPD	1 (20.0)	4 (80)	
Orthopaedic	0 (0.0)	30 (100.0)	
Paediatrics	0 (0.0)	15 (100.0)	
Gynaecology	0 (0.0)	3 (100.0)	
Others	5 (8.9)	51 (91.1)	
Year of request			
2005	4 (8.8)	46 (92.0)	0.892
2006	3 (3.7)	79 (96.3)	
2007	3 (4.9)	58 (95.1)	
2008	2 (8.3)	22 (91.7)	
2009	3 (4.9)	58 (95.1)	
2010	5 (6.6)	71 (93.4)	
Clinical condition			
Polyarthritis	19 (8.2)	214(91.8)	0.252
LBP	0 (0.0)	24 (100.0)	
Fever	1 (5.0)	19 (95.0)	
Routine screen	0 (0.0)	24 (100.0)	
Suspected CTD	0 (0.0)	5 (100.0)	
Knee pain	0 (0.0)	5 (100.0)	
JIA	0 (0.0)	1 (100.0)	
Visual disturb	0 (0.0)	1 (100.0)	
Others	0 (0.0)	60 (100.0)	

N= number, %-percentage, RF-rheumatoid factor, pos-positive, neg-negative, GOPD- general outpatient department, MOPD-medical outpatient department, SOPD-surgical outpatient department, LBP- low back pain, CTD-connective tissue disease, JIA-juvenile idiopathic arthritis

Table 3: Performance of rheumatoid factor test in identifying patients with Musculoskeletal (MSK) diseas

Test	MSK present (n=265)	MSK absent (n=89)	Performance
RF +ve	19	1	Sensitivity- 7.17% (95%CI, 4.37-10.97)
RF -ve	246	88	Specificity- 98.88% (95%CI 93.90% - 99.97%).
			Positive LR - 6.38 (95% CI 0.87, 40.99)
			Negative LR - 0.94 (95% CI 0.90, 0.98).
			PPV - 95.0% (95%CI 77.02, 99.29%)
			NPV - 26.35% (95%CI 25.48, 35.30%).
			Test accuracy - 30.23% (95% CI25.48, 35.30%).

N= number, %-percentage, RF-rheumatoid factor, pos-positive, neg-negative, GOPD- general outpatient department, MOPD-medical outpatient department, SOPD-surgical outpatient department, LBP- low back pain, CTD-connective tissue disease, JIA-juvenile idiopathic arthritis

Frequency of Rheumatoid Factor (RF) tests Positivity.

Rheumatoid factor test was positive in 20 (5.6%) cases of which 14 (70%) were females and 19 (95%) had polyarthritis. Only one (5%) positive case had fever and arthralgia. There was no request made based on standard diagnostic criteria of rheumatic diseases such as the American College of Rheumatology, (ACR)/European League Against Rheumatism, (EULAR), 2019[16]. Rheumatoid factor was significantly associated with the presences of musculoskeletal complaints (p=0.033).

There was no association between positive RF and sex (p=0.352). Those in age group 31 to 40 years, had the highest number of requests made (n=155, 43.8%) and individuals with ages greater than 60 years had higher proportion of positive RF test (16.7%).Majority (14 out of 20, 70%) of cases with positive RF were from GOPD and MOPD. The proportion of cases with positive RF was fairly distributed across the years in which the test was conducted. This is shown in table 2.

After categorizing patients into those with musculoskeletal (MSK) conditions (n=265) and those without MSK (n=89), RF test was significantly associated with presence of MSK (p=0.033) and 95% of all patients with positive RF had MSK disease.

The overall sensitivity of RF test in detecting MSKdisease (polyarthritis in particular)in this study was 7.17% (95%CI, 4.37-10.97) and specificity was 98.88% (95%CI 93.90%, 99.97%). The other performance test is presented in table 3.

DISCUSSION

Our findings indicate that rheumatoid factor (RF) test is frequently requested by general practitioners, especially in patients with polyarthritis. The frequency of positive RF test is 5.6%.Positive RF test was proportionally higher amongst the elderly. There were no documented standard criteria for diagnosis of rheumatic diseases before the request were made by all the physicians. The test was highly specific for excluding patient without polyarthritis but it is less sensitive. This underscores the fact that requesting the test in the absence of florid signs and symptoms of definitive rheumatic disease is not fruitful.[10]

Studies have consistently shown that RF test is predominantly requested by general practitioners in the absence of symptoms suggestive of rheumatic diseases,[4, 5, 12] similar to what we found. The most frequent reason for requesting the test is symmetrical polyarthritis in most studies,[5, 6] however, low back pain and muscle pain were also common indications for the request. Most of the requests in this study were also due to polyarthritis and few requests were due to back pain and a host of other miscellaneous conditions. The absence of standard diagnostics clinical criteria for rheumatic diseases before requesting the test was similar to findings obtained from other studies.[4, 10] Similar findings by Scott et al [13] led them to propose that, a focus on clinical history and examination findings should be the best approach for early referral of patients with suspected rheumatoid arthritis rather than focusing on RF test.

Studies have shown that RF positivity in the general population is less than 4.5%, with similar proportion of males and females,[6-7] but the frequency is higher in population of patients with Rheumatoid arthritis. Our findings of 5.6% of positive RF test was similar to that reported by Miller *et al* [12] and lower than 22% reported by Morsley et al,[4] Miller *et al* [12] also reported that 18% of those with clinical diagnosis of rheumatoid arthritis had positive RF. The high proportion of RF positivity in patients with rheumatoid arthritis proofs that testing for RF is more useful in individuals with symptoms suggestive of rheumatoid arthritis, rather than routine testing of RF.

Rheumatoid factor positivity is frequently seen in the aging population and is partly due to age related immune dysregulation[14]. Patients aged 61 and above in this study had the higher proportion of positive RF test, supporting previous reports.[12, 14-15]

Rheumatic diseases such as rheumatoid arthritis is frequently diagnosed using sets of standard clinical criteria[16]. The clinical utility of RF test adds to the sensitivity and the specificity of these criteria, in addition to prognosticating patients with rheumatoid arthritis.[8]

In this study, the sensitivity of RF test in detecting a patient with musculoskeletal disease was low (less than 8%) and the specificity was high (99%)although the PPV was high (95%) in detecting patients with polyarthritis. This could probably be due to the fact that most of the request were made without proper clinical assessment as to whether the patients qualify to be screened for rheumatic disease or not. Sensitivity and specificity of RF test is higher in patients with Rheumatoid arthritis (greater than 60 and 80% respectively) albeit with low PPV (2.6%).[8,9] Other studies[8,9] have shown that positive RF is an important contributor to the diagnosis of RA if it occurred within the year prior to diagnosis; thus, further elucidating that testing of RF out of clinical context is not useful. The diagnostic utility of RF test in the evaluation of patients without Rheumatic disease has been demonstrated in previous studies to be un-useful when comparing the cost of the test and the positive predictive value of the test.[4,10,13]

The clinical implication of these in-appropriate request are, delay in referring patients to specialist, delay or inability to make diagnosis of rheumatic disease and increased cost of care, especially in developing countries where patients pay out of pocket.

The limitations observed in this study were our inability to access all the

information in some case notes and lack of follow up to see if those tested positive actually developed Rheumatoid arthritis or not. We recommend that physician should only request for RF after thorough clinical evaluation of patients with suspected rheumatic or autoimmune diseases before requesting for RF and a study involving a larger sample size be done to further elucidate our findings.

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