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Original Research Article

Effect of thyroid dysfunction on disease activity of patients with rheumatoid arthritis

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic autoimmune systemic inflammatory multisystem disease of unknown cause that may affect many tissues and organs, but principally attacks synovial joints, primarily affecting the peripheral joints in a symmetrical pattern. The pathology of the disease process often leads to destruction of articular cartilage. It is the commonest inflammatory arthropathy worldwide with a gender predilection towards women. Prevalence of RA in the adult general population is approximately 1%. An association between RA and thyroid dysfunction with or without autoimmune origin has been reported in 6% to 34% of patients with RA. On the contrary, when presence of thyroid antibodies is considered, despite normal thyroid function, the prevalence can rise up to about 38%. These rates are significantly greater when compared with the general population.
Methods: RA patients who were diagnosed according to the new 2010 EULAR/ACR criteria and thyroid function tests were done and patients with thyroid dysfunction were identified and then patients were divided into two groups based on presence of thyroid dysfunction with rheumatoid arthritis and disease activity was illustrated in both groups based on different scales.
Results: In all, 250 patients 215 (86.8%) were females and 33 (13.2%) were males. ESR was elevated in 85 (34%) patients while as it was normal in 165(66%) patients. CRP was positive in 127 (52.7%) negative in 123 (47.3%) patients. Although subclinical hypothyroidism was the most frequent abnormality observed in 38.3% patients, only 30% had concomitant anti-TPO raised and 71.4% patients of overt hypothyroidism had raised anti-TPO antibody. Disease activity parameters were significantly higher in patients of RA with hypothyroidism as compared to other group. Although most of parameters of disease activity showed a higher frequency in the group having patients with thyroid disorder but the swollen joint count was comparable in both the groups and was not statistically significant.
Conclusions: Presence of thyroid disorders in RA patients is suggestive of a more aggressive disease. To diagnose concurrent thyroid disorders at an earlier stage, routine measurement of serum thyroid- stimulating hormone is recommended in all RA patients at the time of diagnosis and with yearly interval thereafter.

Keywords: Autoimmunity, Hypothyroidism, Peripheral joints, Rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune systemic inflammatory multisystem disease of unknown cause that may affect many tissues and organs, but

principally attacks synovial joints, primarily affecting the peripheral joints in a symmetrical pattern.[1] The pathology of the disease process often leads to destruction of articular cartilage.[2] It is the commonest inflammatory arthropathy worldwide with a gender predilection towards women. Prevalence of RA in the adult general population is approximately 1%.[3,4] The worldwide prevalence of autoimmune thyroid disease (AITD) in RA varies considerably, ranging from 0.5% in Morocco to 27% in Slovakia.[3,4] An association between RA and thyroid dysfunction with or without autoimmune origin has been reported in 6% to 34% of patients with RA.[5] On the contrary, when presence of thyroid antibodies is considered, despite normal thyroid function, the prevalence can rise up to about 38%.[4] These rates are significantly greater when compared with the general population (about 2-3 times).[6,7] Routine screening of the population for thyroid disease is not recommended; however, assessment of high-risk group, for example, patients with abnormal findings on physical examination, symptoms suggestive of hyperthyroidism or hypothyroidism, women with a positive family history of thyroid disease, previous thyroid dysfunction, and also a history of other autoimmune disease, for example, type 1 diabetes or Addison disease, has been encouraged.[8]

Previous studies were in favour of the hypothesis that an association between thyroid dysfunction and RA exists, probably due to autoimmunity; however, the results of these studies were not consistent.[9] Furthermore, most of these studies focused on the clinical characteristic of thyroid dysfunction, and just a few of them discussed the impact of thyroid dysfunction on disease activity and treatment response of RA.

The primary objective of this study was to reveal the prevalence of thyroid disorders among RA patients and to find whether thyroid disorders are more prevalent among the RA patients. The secondary objectives of the study were to illustrate the effect of thyroid dysfunction on disease activity of rheumatoid arthritis and response of patients to treatment of thyroid dysfunction.

Aim and objective of research work was to study the effect of thyroid dysfunction on disease activity in rheumatoid arthritis.

METHODS

The present study was conducted in, Government Medical College Srinagar and Associated Hospitals, Jammu and Kashmir, India in patients attending rheumatology/medicine opd clinic. The study was of prospective nature, and analytical cross sectional study. Ethical clearance was taken from the institution. We had included 250 patients in our study based on an anticipated prevalence of thyroid dysfunction among rheumatoid arthritis and an absolute error of 5% with 30% prevalence and 95% confidence level.

Inclusion criteria

The study included patients of rheumatoid arthritis who fulfilled European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR)-2010 criteria for rheumatoid arthritis and were screened for: triiodothyronine (T3), thyroxine (T4), free T4 (free thyroxine) thyroid stimulating hormone (TSH), anti-thyroid perioxidase antibodies (anti-TPO) antibodies.

Exclusion criteria

Patients with history of:

- Surgical removal of thyroid gland,
- Any malignancy on radiotherapy and damage to thyroid,
- Patients on drugs causing hypothyroidism,
- Pregnancy,
- Patients on oral contraceptives,
- Sepsis and serious underlying diseases.

Procedure

Patients attending Outpatient Department of Medicine at SMHS Hospital were evaluated for a history of thyroid disease, use of thyroid drugs or supplementation. Blood samples were obtained for the measurement of thyroxine, triiodothyronine, and thyroid stimulating hormone. Samples of blood were also obtained for the detection of rheumatoid factor and anti-TPO antibody. Taking all aseptic and antiseptic precautions about 3-5 ml of venous blood from median cubital vein was collected in clot activating vacutainer. The blood was collected after 10 to 12hours of fasting. After clot formation, the samples were centrifuged at 4000 rpm to separate serum from the cells.

Serum aliquots were stored at 4°C to be run in batches. The samples were allowed to thaw prior to assay and mixed thoroughly. Hemolysed and lipemic samples were rejected.

Thyroid function test (TFT) T3, T4, FT3, FT4, TSH and anti-TPO were estimated by Chemiluminescent Microparticle Immunoassay (CMIA) method using ABBOTT ARCHITECT i1000 SR analyzer. It is a two-step immunoassay using chemiluminescent microparticle.[10] Immunoassay (CMIA) technology with flexible assay protocols, referred to as chemiflex. Patients with a serum level TSH of 0.35mIU/L-4.2mIU/L was considered as normal. Levels more than or equal to 4.2mIU/L with normal T4 and FT4 levels was considered as subclinical hypothyroidism and patients having raised TSH and low T4, FT4 levels were considered overt hypothyroid. T3 value of 0.6-1.6ng/ml, T4 value of 4.5-11.7ng/dl and FT4 levels of 0.8-1.7 were considered as normal. Anti-TPO estimation was also done Chemiluminescent Microparticle Immunoassay (CMIA) method using ABBOTT ARCHITECT i1000 SR analyzer, for quantitative determination of IgG class of

thyroid antibodies in human serum and plasma on the ARCHITEST iSYSTEM. A value of >5.6ng/ml was taken as positive. Global assessments of disease activity were recorded independently by physician, using the standard 100mm horizontal visual analogue scale (VAS) in which 0 no activity and 100 maximal activity. DAS-28 was calculated in each patient.[11] The following DAS-28 values relate to clinical status:

- Remission: DAS-28- 2.6;
- Low disease activity: DAS-28- 2.6-3.1;
- Moderate disease activity: DAS-28- 3.2-5.1;
- High disease activity: DAS28->5.1.

Statistical analysis

The recorded data was compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as Mean±SD and categorical variables were summarized as percentages. Frequency distribution tables, bar and pie charts were used for data presentation. Chi-square test or Fisher's exact test, whichever appropriate, was used to determine association between various categorical variables. P-value less than 0.05 was considered statistically significant. All P-values were two tailed. Patients were divided into two groups: RA with hypothyroidism (Group A) and RA without hypothyroidism (Group B). The Mann-Whitney U and 2 tests were used to calculate the significance of the median of continuous variables between the two groups, and frequency of discrete variables for non-parametric data, respectively.

RESULTS

The mean age of patients was 49.2±12.1. Most common age group was 37-52 years with 40% patients belonging to this group and next 30% belonging to 53-64 years age group. Out of a total of 250 patients, 215 (86.8%) were females and 33 (13.2%) were males. ESR was elevated in 85 (34%) patients while as it was normal in 165 (66%) patients. CRP was positive in 127 (52.7%) patients while as it was negative in 123 (47.3%) patients. RF was more than 3 times elevated in 154 (61.8%) patients, <3 times raised in 85 (34%) patients and negative in only 11 (4.2%) patients. Anti CCP was more than 3 times elevated in 195 (78.1%) patients, <3 times raised in 16 (6.3%) patients and negative in 39 (16.5%) patients. Anti-TPO antibodies were negative in 195 (78.4%) patients with rheumatoid arthritis and was positive in 54 (22.5%) patients. Although subclinical hypothyroidism was the most frequent abnormality observed in 38.3% patients, only 30% had concomitant anti-TPO raised and 71.4% patients of overt hypothyroidism had raised anti-TPO antibody. Spectrum is illustrated in Table 1.

The patients were divided into two groups based on thyroid dysfunction present or not present and the disease severity was checked in both the groups and results compared as described in Table 2.

Disease activity parameters such as the visual analogue scale for pain, patients' global health assessment score, tender joint count, DAS-28 and ESR were significantly higher in patients of Group A as compared to Group B (Table 2).

Table 1: Spectrum of thyroid dysfunction in rheumatoid arthritis (n=250).

Parameter	Number of patient	%
Subclinical hypothyroidism	96	38.3
Overt hypothyroidism	8	3.9
Subclinical hyperthyroidism	1	0.4
Euthyroid with elevated anti-TPO levels	13	4.8

Table 2: Disease activity.

Parameter	Group A (RA with thyroid dysfunction n=103)	Group B (RA without thyroid dysfunction n=147)	P value
Visual analogue scale	78±12.2	58.6±15	0.002
Patient global assessment score	67.8±3.4	55.4±18	0.0012
Tender joint count	23.6±4.2	17.3±5.5	0.002
swollen joint count	8.3±4.4	5.2±3.4	0.067
DAS-28-ESR	6.7±0.9	5.5±1.0	0.004
Low disease activity.	1(1%)	50(34%)	0.977
Moderate disease activity	5(5%)	41(28.1%)	0.090
High disease activity	97(95%)	69(37%)	0.0002

Although most of parameters of disease activity showed a higher frequency in the group having patients with thyroid disorder but the swollen joint count was comparable in both the groups and was not statistically significant. No patient in our study was in remission. low disease activity according to DAS28 scores was more

frequent in group B. Moderate disease activity was found in 5 patients whereas high disease activity was found in 97 patients. Group A had a higher number of high disease activity patients as compared to group B; however, the difference in frequency was statistically significant (P=0.0002). ESR levels were found significantly increased in high disease activity patients than that of moderate disease activity patients with p value of 0.004. we did a multinomial logistic regression analysis to see the independently associated variables with Group A and Group B as dependent variables. All the variables found significantly associated in univariate analysis were used as independent variables and stepwise model was used for the analysis. VAS was observed significantly independently associated with hypothyroidism in RA when compared from patients with RA only. We performed Linear regression to see the independent factors associated with TSH level in a stepwise manner and we observed that ESR and tender joint count were independently significantly positively correlated with TSH levels in RA patients as shown in Table 3.

Table 3: Linear regression analysis with TSH levels as dependent variable in ESR and tender joint count.

Variable	P value	Standardized coefficient beta	95%cl
ESR	0.004	0.369	0.169-0.711
Tender joint count	0.002	0.362	0.094-0.459

DISCUSSION

Rheumatoid arthritis has been an important research area due to the nature of disease and due to autoimmunity which is the cause of association with other autoimmune diseases as autoimmune disorders run parallel. A similar association between RA and hypothyroidism has been demonstrated since the 1960s.[11,12] One of the first studies reported thyroiditis in up to 12% of patients with RA.[13] Our study also shows a similarly high incidence (42.2%). Most common thyroid dysfunction observed was subclinical hypothyroidism seen in 38.3% of the patients when compared to general population in the same geographical area, Kashmir our results were two times higher (Hamid Bashir and others 21.56%, Rama Jailkhani and others 33%).[14,15]

The results of our study were similar to the study done by Tekaya R and others in Tunisia who found that thyroid abnormalities were detected in 40% of the patients.[16] we measured the disease activity using DAS-ESR score and VAS and we found significant correlation between serum levels of TSH and disease activity parameters (ESR and DAS-28), as did the study by Elattar et al.[3] The comparison between two groups created in patients based on presence or absence of thyroid dysfunction showed disease activity parameters such as the visual analogue scale for pain, patients' global health assessment score, tender joint count, DAS-28 and ESR were significantly higher in patients of thyroid dysfunction group as compared to patients of normal thyroid functions. Swollen joint count was also higher in first group but this difference was not statistically significant the results where correlating with study done by Prakash Joshi et al.[17]

CONCLUSION

The conclusion which we derived from this study was not only thyroid dysfunction is more frequent in rheumatoid arthritis but it has a very significant impact on the disease activity and patients who are a diagnosed case of rheumatoid arthritis should be screened for thyroid dysfunction if minimal symptoms of same are suspected. The recommendations are further extended to patients having high disease activity should routinely screened for thyroid dysfunction. Both the disorders should be managed spontaneously and hit early and hit hard should be the minimum possible goal.

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