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THE STUDY OF THYROID FUNCTION IN RHEUMATOID ARTHRITIS IN NORTH BIHAR

Physiology

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ABSTRACT

RA patients coming from North Bihar reason i.e. Darbhanga, Madhubani, Samastipur etc. at DMCH, OPD. The study was of prospective nature, and analytical cross sectional study.The relationship between thyroid function and rheumatoid arthritis (RA) is a debatable subject and many studies have successfully demonstrated the autoimmune nature of thyroid dysfunction in RA.

In a systematic review analyzing the results of 54 studies that investigated the coexistence of ADs within individuals and 9 studies that examined within-family associations, these data supported an increased prevalence of ATDs among patients with RA. In a separate study investigating the frequency of rheumatic diseases in patients suffering from ATDs, various rheumatic diseases were detected in 62% of patients with ATDs, one of which wasRA.

The combination of RA and autoimmune thyroiditis was already recognized half a century ago. More recently, the coexistence of RA and hypothyroidism was reassessed, but data on this relationship remains sparse. As hypothyroidism and RA are both relatively common autoimmune diseases associated with increased CVD morbidity and mortality.Further research into the interaction between these two diseases is worthwhile, both from a cardiovascular and from an immunological point of view.

KEYWORDS

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by a symmetrical inflammation of the synovium, resulting in tenderness and destruction of bone and cartilage in various joints, particularly the smaller joints of the hands and feet. Although the cause of RA is unknown, autoimmunity plays a pivotal role in its chronicity and progression. RA affects approximately 1.0% of the general population, women more often than men, and theinflammatory burden of the disease results in functional disability. Several contributors to RA pathogenesis have been identified in recent years: genetic factors (shared epitope on locus *HLA- DRB1*, but also *PTPN22, STAT4, 6q23* and *TRAF1/C5*), cigarette smoking, auto antibodies (rheumatoid factor (RF), anti-cyclic citrullinated protein antibodies (ACPA)), infectious agents, as well as nutritional and hormonal factors. Ultimately, an interplay between these endoge- nous and exogenous factors has been postulated to break immunological tolerance and trigger the immunological response that manifests itself as RA. The immunological activation of RA leads to infiltration of the synovium by an orchestra of immune cells like T and B cells, macrophages, dendritic cells and fibroblast-likesynoviocytes, contributing to the proliferation of cell tissue (i.e. pannus formation) and neovascularization. These immunological processes perpetuate syste- mic inflammatory responses, leading to a chronic, disabling disease which results in the inability to work and an impaired quality of life.

It has been widely observed that disorders with an autoimmune pathogenesis occur with increased frequency in patients with a history of another autoimmune disease (AD). The number of documented cases of a co-occurrence of different autoimmune diseases in a single patient have increased in recent years.

Autoimmune thyroid disease (ATD) in the form of Hashimoto's thyroiditis and Graves' disease are all organ-specific. Autoimmune hypothyroidism is considered the most common autoimmune disease and its prevalence has been estimated to be up to 2%, with a higher concentration in older women. ATD is characterized by the presence of antibodies against thyroglobulin, thyroid peroxidase, or thyrotropin receptor autoantigens. The relationship between RA and the thyroid gland has been studied extensively, with several studies demonstrating the autoimmune nature of thyroid dysfunction inRA.

AIMS AND OBJECTIVES

To study prevalence of thyroid function in rheumatoid arthritis patients in North Bihar.

MATERIALAND METHODS

The present study was conducted in Department of Physiology associated with Department of Medicine, Darbhanga Medical College and Hospital, Laheriasarai, Bihar over a period of 3 months in patients comes from Darbhanga, Madhubani, Samastipur attending OPD, DMCH. The study was of prospective nature, and analytical cross sectional study. Ethical clearance was taken from the institution. We included 385 patients into the study based on an anticipated prevalence of thyroid dysfunction among rheumatoid arthritis and an absolute error of 5% with 30% prevalence and 95% confidencelevel.

Sample size was calculated based on these parameters:

$$\text{Sample size } N = \frac{4 \times 30 \times 70}{5 \times 5} = 336$$

Considering a non-response rate of 15%.
Total sample size needed =385

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 (T_3), thyroxine (T_4), free T_4 (free thyroxine) thyroid stimulating hormone (TSH), anti-thyroid perioxidase antibodies (anti-TPO) antibodies.

EXCLUSION CRITERIA

Patients with history of:

1. Surgical removal of thyroidgland.
2. Any malignancy on radiotherapy

3. Patients on drugs causinghypothyroidism.
4. Pregnancy
5. Patients on oral contraceptives
6. Sepsis and serious underlyingdiseases and damage tothyroid.

METHODOLOGY

Patients attending Outpatient Department of Medicine at DMCH 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 12 hours of fasting. After clot formation, the samples were centrifuged at 4000 rpm to separate serum from thecells.

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 Immunoassay (CMIA) technology with flexible assay protocols, referred to as chemiflex. Patients with a serum level TSH of 0.35 mIU/L - 4.2 mIU/L was considered as normal. Levels more than or equal to 4.2 mIU/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 0.6-1.6 ng/ml, T4 value of 4.5-11.7 ng/dl and FT4 levels of 0.8-1.7 were considered asnormal.

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.

STATISTICALANALYSIS

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 aspercentages. 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.

RESULTS AND DISCUSSION

The mean age of patients was 48.2±12.1. Most common age group was 35-49 years with 38.4% patients belonging to this group and next 30.1% belonging to 50-64 years age group. Out of a total of 385 patients, 334 (86.8%) were females and 51 (13.2%) were males.

ESR was elevated in 89 (23.1%) patients while as it was normal in 296 (76.9%) patients.

CRP was positive in 199 (51.7%) patients while as it was negative in 186 (48.3%)patients.

RF was more than 3 times elevated in 238 (61.8%) patients, ≤3 times raised in 131 (34%) patients and negative in only 16 (4.2%)patients.

Anti CCP was more than 3 times elevated in 300 (77.9%) patients, ≤3 times raised in 25 (6.5%) patients and negative in 60 (15.6%) patients.

Table 1 : Thyroid function test among of the study patients (n=385)

Thyroid function test		No. of Patients	Percentage
TSH	<0.35	3	0.8
	0.35-4.2	210	54.5
	>4.2	172	44.7
T3	<0.6	13	3.4
	0.6-1.6	362	94.0
	>1.6	10	2.6
T4	<4.9	42	10.9
	4.9-11.7	336	87.3
	>11.7	7	1.8
FT4	<0.8	21	5.5
	0.8-1.7	326	84.7
	>1.7	38	9.9

Anti-TPO antibodies were negative in 302 (78.4%) patients with rheumatoid arthritis and was positive in 83 (21.5%) patients shown in table 2.

Table 2 : Distribution of anti-TPO among study patients (n=385)

Anti-TPO	No. of Patients	Percentage
Negative	302	78.4
≤3 times elevated	2	0.5
>3 times elevated	81	21.0
Total	385	100

The most common thyroid dysfunction observed was subclinical hypothyroidism in 146 (37.9%) patients with elevated TSH and normal Free T4 levels. Overt hypothyroidism was seen in 14 (3.6%) patients and only a single patient (0.3%) was found to be hyperthyroid. Twenty (5.2%) patients were found to be euthyroid but had elevated anti-TPO antibodies. Total thyroid dysfunction was found in 41.8% patients as illustrated in table 3.

Although subclinical hypothyroidism was the most frequent abnormality observed in 37.9% patients, only 30% had concomitant anti-TPO raised and 71.4% patients of overt hypothyroidism had raised anti-TPOantibody.

Table 3 : Spectrum of thyroid function in rheumatoid arthritis (n=385)

Parameter	No. of Patients	Percentage
Subclinical Hypothyrodism	146	37.9
Overt Hypothyroidism	14	3.6
Subclinical Hyperthyroidism	1	0.3
Euthyroid with elevated anti-TPO anti bodies	20	5.2

Table 4 : Association between different variables (RF and Anti CCP) with the thyroid disturbance status in RA patients

			RF		Total	P-value	Anti CCP		Total	P-value
			Normal	High			Normal	High		
Subclinical Hypothyroidism	Yes	N	1	145	146	0.007*	25	25	121	0.513
		%	0.7	99.3	100		17.1	17.1	82.9	
	No	N	15	224	239		35	35	204	
		%	6.3	93.7	100		14.6	14.6	85.4	
	Total	N	16	369	385		60	60	325	
		%	4.2	95.8	100		15.6	15.6	84.4	
Overt Hypothyroidism	Yes	N	0	14	14	1.000	2	2	12	1.000
		%	0	100	100		14.3	14.3	85.7	
	No	N	16	355	371		58	58	313	
		%	4.3	95.7	100		15.6	15.6	84.4	
	Total	N	16	369	385		60	60	325	
		%	4.2	95.8	100		15.6	15.6	84.4	
Hyperthyroidism	Yes	N	0	1	1	0.835	0	0	1	1.000
		%	0	100	100		0	0	100	
	No	N	16	368	384		60	60	324	
		%	4.2	95.8	100		15.6	15.6	84.4	
	Total	N	16	369	385		60	60	325	
		%	4.2	95.8	100		15.6	15.6	84.4	

Table (4 and 5) shows RF was elevated in patients with overt hypothyroidism and in single patient with hyperthyroidism but it was not statistically significant. Similarly anti-CCP was more frequently elevated in patients with thyroid dysfunction. On the other hand, ESR and CRP were low in patients with thyroid abnormality. When the association between different inflammatory markers and thyroid function test was studied, it was observed that RF was significantly elevated in patients with subclinical hypothyroidism and the association was statistically significant with a p value of 0.007.

Table 5 : Association between different variables (CRP and ESR) with the thyroid disturbance status in RA patients

	RF		Total	P-value	Anti CCP		Total	P-value
	Normal	High			Normal	High		

Subclinical Hypothyroidism	Yes	N	79	67	146	0.075	118	28	146	0.152
		%	54.1	45.9	100		80.8	19.2	100	
	No	N	107	132	239		178	61	239	
		%	44.8	55.2	100		74.5	25.5	100	
	Total	N	186	199	385		296	89	385	
		%	48.3	51.7	100		76.9	23.1	100	
Overt Hypothyroidism	Yes	N	9	5	14	0.280	13	1	14	0.204
		%	64.3	35.7	100		92.9	7.1	100	
	No	N	177	194	371		283	88	371	
		%	47.7	52.3	100		76.3	23.7	100	
	Total	N	186	199	385		296	89	385	
		%	48.3	51.7	100		76.9	23.1	100	
Hyperthyroidism	Yes	N	1	0	1	0.483	0	1	1	0.231
		%	100	0	100		0	100	100	
	No	N	185	199	384		296	88	384	
		%	48.2	51.8	100		77.1	22.9	100	
	Total	N	186	199	385		296	89	385	
		%	48.3	51.7	100		76.9	23.1	100	

CONCLUSION

Thyroid dysfunction is prevalent in patients with rheumatoid arthritis with percentage of 41.8%, subclinical hypothyroidism is the most common thyroid dysfunction encountered (37.9%) followed by overt hypothyroidism (3.6%), hyperthyroidism is very rare seen only 0.3% patients. The results of our study were similar to the study done by Rawdha Tekaya and others[29] in Tunisia who found that thyroid abnormalities were detected in 40% of the patients. In another study done by Enas A Ellatar and others, hypothyroidism was the most frequent abnormality detected in 24%, followed by subclinical hypothyroidism (4%) whereas hyperthyroidism was seen only in 1.3% ofpatients.

Regular screening of patients is recommended. Prevalence of thyroid disorders in rheumatoid arthritis patients was found to be significantly related to rheumatoid factor status, but no significant correlation was seen in other variables like ESR, CRP, anti-CCP. The increased prevalence of anti-TPO in patients with normal thyroid function may also serve as a marker that precedes and heralds the development of overt disease in near future; hence we recommend screening for anti-TPO antibodies in this population.

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