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"Correlation Between Autoimmune Thyroid Disease, Rheumatoid Factor And Vitiligo in Hypothyroid Patients In Ranchi, Jharkhand."

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Abstract :
Introduction :*Iodine deficiency lead to hypothyroidism, autoimmune attack to thyroid gland may also result in the same, excess iodine supplementation is supposed to induce autoimmune injury to thyroid gland. Rheumatoid arthritis (RA), in turn, is a chronic, complex, and heterogeneous autoimmune disease, in which there is a response directed towards the diarthrodial joints producing symmetric polyarthritis with progressive damage to the joints, bone destruction, and extra-articular manifestations (EAMs) such as cutaneous nodules, lung involvement, cardiovascular disease (CVD), episcleritis, and so forth, the autoimmune hypothesis as its cause is most commonly accepted. Vitilgo is also caused by autoimmunity, circulating anti-melanocyte antibodies that target various melanocyte antigens- tyrosinase, tyrosine related proteins, dopachrome tautomerase, and others that have the capability to kill melanocyte in vitro. A person presenting with all these three disease of autoimmune origin can be categorised as a patient of multiple autoimmune syndrome. This study hypothesises that some possible pathogenic linkages exist between these three distinct Autoimmune disease.*
Objective:*To* assess the correlation and association of the three autoimmune diseases, autoimmune thyroid disease, rheumatoid arthritis and vitiligo in randomly selected hypothyroid patients.
Methodology: *Study design:- A cross sectional descriptive study.100 patients of hypothyroid were selected on the basis of their TSH level . Blood sample were taken and screened for the presence of anti TPO antibody and Rheumatoid factor.Patients were also examined for the presence of vitiligo.*
Result: *Significantly higher mean rank of TSH and anti TPO antibody is associated with patients reactive to Rheumatoid factor than non reactive but vitiligo is not significanly associated with higher values of TSH and anti TPO antibody.*
Conclusion: *Patients presenting with any one or two component of a multiple autoimmune syndrome should be screened for the other component as they share some common mechanism and are prone to appear in future.*
Keywords: *Anti TPO, Hypothyroidism, Polyautoimmunity, RA factor, Vitiligo.*

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I. Introduction

Autoimmune thyroid disease is a term used to bring together a group of pathologies that has thyroid dysfunction and an autoimmune response against this endocrine organ as its hallmark. [1,2] This group of pathologies exhibits an autoantibody profile that may be composed of (1) antibodies directed against the thyroid peroxidase enzyme (TPOAb), (2) antibodies directed against thyroglobulin protein (TgAb), and (3) antibodies directed against thyrotropin receptor (TSHrAb). Furthermore, there is a T or B lymphocytic response that prevails and ultimately, this will define the pathology that becomes manifest. Generally, T lymphocytes are the main cell type infiltrating the gland in Hashimoto's thyroiditis(presenting as hypothyroidism).[3] Prevalence of autoimmune disease has been described of 5 to 15% in women and 1–5% in men. Hollowell et al[4] described a prevalence of 13% for TPO Ab and 11.5% for TgAb among the general population. Autoimmune thyroid disease can be regarded as the most common autoimmune endocrine disease.[5] All of these autoimmune diseases lead to disability,[6,7] an increase in co-morbidities,[8] and premature mortality.

For several autoimmune diseases, an increased occurrence of thyroid disorders in patients suffering from RA has been documented—both autoimmune and non-autoimmune in nature.[9,10] Similarly, in autoimmune disease spectrum, rheumatologic and non-rheumatologic manifestations of autoimmunity in autoimmune thyroid disease have been described.[11] Autoimmune diseases share similar mechanisms.[12,13] In clinical practice some conditions support these commonalities. One of these corresponds to polyautoimmunity, which is defined as the

presence of more than one autoimmune disease in a single patient.[14] Patients with polyautoimmunity or multiple autoimmune syndrome may have a modified disease course (with a worse prognosis or a better one) and a modified clinical presentation. Moreover, first degree relatives of these patients are at increased risk of developing an autoimmune disease.[15] Several studies have consistently mentioned association and clustering between autoimmune diseases.[16,17] Recently some studies have seen the emergence and establishment of antibodies to citrullinated antigens as the primary diagnostic marker for rheumatoid arthritis. Recent work has established the close link between genetic factors, environmental factors and the presence of these antibodies. The researchers have therefore examined these relationships in another serological subgroup with rheumatoid arthritis. Autoimmune thyroid disease is reported in up to 30% of patients with rheumatoid arthritis. Like rheumatoid arthritis, autoimmune thyroid disease has also been associated with a combination of genetic and environmental influences.[18,19]

Vitiligo is one of disorders of melanin pigmentation that affects approximately 0.5–2% of the population.[20] It is characterized by depigmentation of varying sizes or shapes with a tendency to progress. Depending on the lesions, vitiligo can be classified into two main categories: generalized and localized. Although the pathogenesis of vitiligo is not yet fully understood, the autoimmune hypothesis is the most commonly accepted.[21.22]

Hypothyroidism is believed to be a common health issue in Jharkhand, as in India, and worldwide. However, there is a paucity of data on the prevalence of hypothyroidism in adult population of Jharkhand. Moreover the cause of Hypothyroidism in patients attending RIMS OPD and admitted in wards are still due to iodine deficiency or autoimmune thyroid disease is still not known as it has been long since the population is using food fortified with iodine. We also tend to find out the association of autoimmune thyroid disease and other common autoimmune disorders like rheumatoid arthritis and vitiligo. The aim of this study was to determine whether vitiligo and Rheumatoid arthritis is statistically significantly associated with thyroid autoimmunity.

II. Methodology

This cross sectional descriptive study has been conducted in the department of Biochemistry, Rajendra Institute of Medical Sciences, Ranchi. The study was granted clearance from Ethical Committee, RIMS, Ranchi. The period of study was from December 2013 to November 2015.A total of 100 cases were studied. The study subjects were assigned by various departments of RIMS for thyroid profile testing and whose Thyroid Stimulating Hormone >6 mIU/mL.

Inclusion Criteria: 1. Patients attending RIMS OPD or inpatients admitted in wards. 2. Age :18-70 years. 3. Sex : either male or female. 4. Should be fasting for at least 12 hours. 5.Should readily agree to participate in the study with an informed consent.

Exclusion Criteria: 1. Non cooperative subjects. 2. Subjects suffering from known liver disease, cardiac disease, renal disease, respiratory diseases or any severe chronic illness. 3. Post radiation/surgical hypothyroidism patients, cancer.

4. Subjects suffering from AIDS.

Study Tools:- 1. Consent from the subject 2. Measurement of Anthropometric parameters. 3. Collection of blood samples:- an overnight fasting blood with caution to avoid haemolysis and contamination. 4. Processing and biochemical analysis of blood samples:- 5. Thyroid Stimulating hormone(TSH) and Anti TPO was analysed by ARCHITECT I Chemiluminescent Microparticle Immunoassay (CMIA). The data and result obtained were statistically analyzed using SPSS software version 20. Mean rank of TSH and anti TPO antibody was calculated in patients reactive to rheumatoid factor and patients presenting with vitiligo and the value were analysed using Mann-Whitney U, Wilcoxon W and Pearson's correlation coeficient was also calculated.

III. Result

1. The mean rank of TSH in the population reactive for Rhematoid factor was 63.06 and in population non reactive for Rhematoid factor was 47.74 The difference mean ranks in the two groups was found significant with P= 0.043 (<.05) and the Z score being -2.028, which is also statistically significant. TSH level is significantly associated with Reactive Rhuematoid Factor.
2. The mean rank of Anti- Thyroid Peroxidase Antibodies in the population reactive for Rhematoid factor was 88.47and in population non reactive for Rhematoid factor was 42.16 the difference in the mean ranks of the two groups was found highly significant statistically with P= 0.000 (<.05) and the Z score being -6.133, which is also statistically significant. Anti- Thyroid Peroxidase Antibodies level has highly significant association with Reactive Rhuematoid Factor.
3. The mean rank of Thyroid Stimulating hormone and Anti- Thyroid Peroxidase Antibodies in the population with vitiligo was 52.55 and 64.00 respectively, and in normal population was 50.25 and 48.33, the difference of the mean rank in the two groups was found not significant statistically with P= 0.804 for TSH

(>.05) and P= 0.102 for Anti-TPO (>.05) the Z score being -.248 and -1.636, which is also not significant. Vitiligo does not have significant relation to raised TSH and Anti-TPO.

4. The Study group showed Positive Anti TPO antibodies in 68% (n=68), reactive Rhuematoid Factor in 18%,(n=18),and 11% of the subjects suffered from Vitiligo.
5.

Table.1 TSH mean rank association withreactive and non reactive RA factor

	RA factor	N	TSH	Mean Rank	Sum of Ranks
	Non reactive	82		47.74	3915.00
	Reactive	18		63.06	1135.00
Total		100			

Table.2 Anti TPO mean rank association with reactive and non reactive RA factor

	RA factor	N	Anti TPO	Mean Rank	Sum of Ranks
	Non reactive	82		42.16	3457.50
	Reactive	18		88.47	1592.50
Total		100			

Table.3 Mean rank of Anti TPO and TSH association with vitiligo

	VITILIGO	N	Mean Rank	Sum of Ranks
Anti Tpo	Absent	89	48.83	4346.00
	Present	11	64.00	704.00
	Total		100	
TSH	Absent	89	50.25	4472.00
	Present	11	52.55	578.00
	Total		100	

IV. Discussion

Earlier it was thought that the major cause of hypothyroidism was iodine deficiency. After the global implementation of iodine fortification steps, we have now come to an era where we find an increasing evidence that the occurrence of thyroiditis is related to iodine supplementation. When mice of an autoimmunity-prone strain were first fed on iodine-deficient diet followed by an iodine-excessive diet, they developed ultrastructural thyroid epithelial cell damage in a dose-dependent manner suggestive of autoimmune disease. The incidence of thyroiditis as well as the degree of lymphocytic infiltration in the thyroid increased gradually, dose-dependently three mechanisms have been assumed for the development of iodine-induced autoimmune thyroiditis. First, iodine intake increases the immunogenicity of thyroglobulin (Tg), thereby precipitating an autoimmune process at both the T- and B-cell level. Secondly, iodine has a toxic effect on thyroid cells. Thirdly, iodine directly stimulates immune and immunity-related cells.[23,24,25] This study suggests that the average TSH in the population was higher, thus pointing towards primary rather than secondary etiology, and median TPO was far from normal , suggesting cause the hypothyroidism being autoimmune in nature. Studies in the recent past have also shown that in the present scenario majority of hypothyroid patients suffer from autoimmune thyroiditis. This is consistent with the findings of Davies TF, Amino M *et al.* [26] Yiqian Luo *et al* proposed that iodine excess is a precipitating environmental factor in the development of autoimmune thyroid disease, while intrathyroidal depletion of iodine prevents disease in animal strains susceptible to severe thyroiditis. The PTPN22 gene encodes lymphoid tyrosine phosphatase (LYP) protein. LYP, through interactions with regulatory kinases such as Csk, appears to act as an inhibitor of the signal cascade downstream from the T-cell receptor. A specific polymorphism associated with a tryptophan substitution for arginine at position 620 (R620W) blocks LYP's interaction with Csk. This polymorphism has been associated with type 1 diabetes, rheumatoid arthritis, systemic lupus erythematosus (SLE), Graves' disease, vitiligo , and weakly associated with Addison's disease.

This study shows a high prevalence of anti- TPO antibodies in patients with hypothyroidism 68%. This is supported by the studies by A, Seaman HE, Wright JW, de Vries CS *et al.* 18 out 68, (26.7%) patients suffered from AITD were reactive to Rhuematoid factor in this study. The studies by Vaidya *et al* showed 36 % prevalence of Rhematoid Arthritis in patients of AITD which is close to our study, and mechanism suggested by Vaidya was the association of *CTLA4* gene. Emina Kasumagic-Halilovic et al, 2011, showed anti-TPO were positive in 64.24% vitiligo patients, and Shriya Dave et al,2003 found 57.1% of the cases of vitiligo suffering from AITD which is close to our sudy as anti TPO was positive in 68%, (n=68) of subjects in the study group.

Currently circulating autoantibodies against various melanocyte's antigen are thought to reflect secondary humoral responses to melanocyte destruction. This theory is supported by the clinical association of vitiligo with autoimmune disorders, the frequent detection of circulating autoantibodies to surface and

cytoplasmatic antigens of melanocytes.[21,22] Furthermore, there are findings of activated T cells in the periphery of actively progressing lesions in some vitiligo patients.[22] Thyroid functional disorders and autoimmune thyroid diseases have been reported in association with vitiligo, and it seems that the incidence of clinical and subclinical thyroid involvement is more common in vitiligo patients than healthy subjects.[27,28] Our study was consistent with the study by L Hegedüs et al, 1994, and H Niepomniszcze et al,2001 suggesting that the autoimmune hypothesis for vitiligo is the most commonly accepted one. Thyroid functional disorders and autoimmune thyroid diseases have been reported in association with vitiligo, and it seems that the incidence of clinical and subclinical thyroid involvement is more common in vitiligo patients than healthy subjects. Hence we should not forget to screen any patient coming to health facility with vitiligo for other autoimmune diseases.

V. Conclusion

It was observed that in the study most subjects had high frequency of raised Anti TPO antibodies, some among them were reactive rheumatoid factor antibody, and few had vitiligo, suggesting common autoimmune pathogenesis.Our findings are in agreement with most of the studies by various researchers. In this study, we aimed to draw attention to these potential coincidences and the possible pathogenic linkages between three distinct Autoimmune Diseases in various individuals diagnosed with rheumatoid arthritis, autoimmune thyroid disease and vitiligo. A patient presenting with any of the above two disease should be screened and followed up for the third one as there is increased probability of its development in future. The increasing number of reports of the co-occurrence of autoimmune diseases indicates the need for continued surveillance for the development of new autoimmune diseases in predisposed patients. Further documentation of observations of possible coincidences of various autoimmune disorders are required in order to yield results that may shed light on the biological pathways of these diseases.

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