Section: Medicine

Research Article

THYROID DYSFUNCTION IN HIV INFECTED PATIENTS AND ITS CORRELATION WITH HAART-A STUDY IN RIMS HOSPITAL

Mayanglambam Bijoy[1], Laimayum Romesh Sharma[1], Huidrom Manimohon Singh[2]

[1]Assistant Professor, Department of Medicine, Regional Institute of Medical Sciences, Imphal, Manipur, India
[2]Senior Resident, Department of Medicine, Regional Institute of Medical Sciences, Imphal, Manipur, India

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Corresponding Author:
Dr. Laimayum Romesh Sharma,
Email: drromeshpushpanjali@gmail.com

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Abstract

Background: HIV infection is a multisystem disease involving endocrine glands. Alteration in thyroid function occurs in HIV infection as well as in patients receiving HAART. The aim of this study was to assess thyroid dysfunction in HIV infected patients and its correlation with HAART. **Materials and Methods:** This cross-sectional comparative study was conducted on 250 HIV positive patients attending ART centre RIMS, Imphal. Thyroid dysfunction was categorized as Hypothyroid, Subclinical Hypothyroid, hyperthyroid, Subclinical hyperthyroid and Sick euthyroid. Data collected were analyzed using SPSS-version-16. Numerical/continuous variables are reported as Mean ± SD (standard deviation). Spearman's correlation coefficient rho "ρ" is used as a non-parametric test to assess association between thyroid dysfunction and HAART therapy. **Result:** A total of 250 HIV positive patients were recruited in the study. Sick euthyroid (17.2%) was commonest thyroid dysfunction. The prevalence of thyroid dysfunction was higher in HIV patient taking HAART than without HAART. There was a Positive correlation between thyroid dysfunction and CD4 count. **Conclusion:** Thyroid function abnormalities are common in HIV patients with HAART or without HAART therapy. Sick Euthyroid is the commonest thyroid function abnormality.

INTRODUCTION

HIV infection is a multisystem disease. The change in the thyroid function tests in HIV is specific and are consistent with an abnormal response to acute illness.[1,2] A high rate of thyroid dysfunction in asymptomatic subjects has been described in HIV, most well described are reduction in free thyroxine (FT4) and free tri-iodothyronine (FT3) and elevated thyroxine binding globulin (TBG) and thyroxine stimulating hormone (TSH) levels.[3,4] Frequently there is progressive elevation of serum TSH and serum TBG concentration in conjunction with low T4 which correlated with cluster differentiation 4 (CD4) cell depletion in AIDS patients.[5]Various mechanisms have been proposed to explain abnormalities in Thyroid Function Test (TFT).[6] These include direct infection of the thyroid gland by opportunistic organisms such as pneumocystiscjirovecii, infiltration of gland bytumours such as Kaposi sarcoma, effect of humoral factors such IL-1 α and TNF- α,side effect of drugs used in the course of HIV infection such as rifampicin, ketoconazole, steroids, and direct infection of gland by HIV. During antiretroviral therapy, the prevalence of two generally asymptomatic conditions subclinical hypothyroidism and isolated low free thyroxine levels is increased.[7] Patients with HIV infection, who are on HAART (Highly active antiretroviral therapy), achieve restoration of previously compromised immune function, resulting in decreased mortality and morbidity from opportunistic infections.[8] However a minority of patients might experience a paradoxical clinical decline as a result of immune reconstruction inflammatory syndrome (IRIS) following HAART.[8] Graves' diseases which is resulting from immune restoration has had relatively recent recognition and might be viewed as a consequence of organ –specific autoimmunity during the late period of T –Cell repopulation, of CD4 positive naïve cells.[9] Earlier studies found that TPO antibodies and TSH receptor antibodies appeared after CD4 T Cells had dramatically increased on HAART, whereas they were repeatedly absent prior to HAART.[9] And Graves' diseases in some reports was closely associated with the rise in TSH receptor antibodies.[9,10] It may also be associated with interferon (INF□) used to treat hepatitis C and interleukin 2(IL-2) therapy in the setting in HIV . A

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close relation exists between serum thyroid hormone levels and nutritional status in HIV infected patients.[11] There is decreased level of FT3 in poorly nourished HIV patients, called as euthyroid sick syndrome; which is the most probable mechanism which cause decreased FT3 in HIV patients. The serum concentrations of T3 decrease only in severely affected HIV patients as T3 is mainly influenced by protein compartments and it can also be due to increased production of tumour necrosis factor (TNF) in HIV infection. CD4 count has been closely correlated with thyroid dysfunction in HIV patients. In Indian sub-continent, there is paucity of studies which need to evaluate the thyroid function in HIV infected patients and their clinical co-relation with CD4 count. Manipur being the state having the highest prevalence rate of HIV (1.40%) in India, so this study was undertaken at Anti Retroviral Therapy(ART) OPD of RIMS Hospital, Imphal with the objective to evaluate the thyroid dysfunction in HIV infected patients.

MATERIALS AND METHODS

The study was Cross-section study carried out in the Anti Retro Viral Therapy (ART) OPD, in Department of Medicine, Regional Institute of Medical Sciences (RIMS) Imphal, Manipur. Study was conducted from October 2011 to August 2013. The sample size for the study was 234 HIV infected patients.

Inclusion criteria

Confirmed cases of HIV infected patients as per NACO (National AIDS Control Organization) of India guideline of 2007 irrespective of HAART.

Exclusion Criteria

Subjects with thyroid or endocrine dysfunction, renal failure, liver failure, chronic infection like hepatitis B and C and acute systemic infection likely to affect thyroid function.

Study tools

Semi-structural interview schedule including Socio-demographic profile including the patients age, gender, weight, height, occupation, religion, marital status, intercurrent illness, IVDU (intravenous drug user), blood transfusion & exposure to unprotected sex with unknown person, parenteral HIV status, the duration of known HIV infection, type and duration of HAART, presence of hepatitis B and C infection were noted carefully. Thyroid function test (TFT): serum total triiodothyroxine (T3), total thyroxine (T4) and TSH (thyroid stimulating hormone) were measured by ELISA test by Human, Germany kit .Various thyroid dysfunction were defined as :Hypothyroid: TSH>4.3 mu/L total T4<4.5 µg/dl or FT4<12 pmol/L, Hyperthyroid : TSH<0.02 mu/L total T4>10.7 µg/dl or FT4>22 pmol/L,Sub clinical hypothyroid: TSH>4.2 mu/L and normal T3 T4, Sub clinical hyperthyroid: TSH<0.02 mu/L and normal T3 T4.Sick Euthyroid: TSH normal and low FT3.CD4 count was done by flow cytometry method by FACS machine . The study population was divided into three (3) categories according to the CD4 count. Category A: CD4 count below 200/mm3.Category B: CD4 count 200 - 350/mm3.Category C: CD4 count above 350/mm3.Hepatitis B and Hepatitis C virus antibody by S.D. HCV ELISA. Other haematological and laboratory tests like Random Blood Sugar (RBS), Liver Function Test (LFT), Kidney Function Test (KFT), complete haemogram were done.

Statistical analysis:

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) 16.0 version. Numerical/continuous variables are reported as Mean ± SD (standard deviation) and for qualitative/categorical variables are again described as number of cases and percentages. The group's means are compared by Independent Sample test (t-test) and □2-test is applied for categorical variables. Spearman's correlation coefficient rho "ρ" is used as a non-parametric test to assess association between thyroid dysfunction and HAART therapy as well as between thyroid dysfunction and CD4 count.

RESULTS

There were143(57.2%) males and 107(42.8%) female in the study. Thyroid function abnormalities in the study subject on HAART is 86(68.8%) which was higher than not on HAART 67(53.6%) [Table 1]. Sick Euthyroid was found to be commonest thyroid dysfunction 17.2%, Subclinical hypothyroid (15.6%), Hypothyroid (0.80%) and the least pertaining to hyperthyroid and sub clinical hyperthyroid with prevalence of 0.40%) [Table2].

Table 1: Thyroid function abnormalities on treatment status.

Age (yr)	HAART			No HAART		
	Female	Male	n=125 Total	Female	Male	n=125 Total
14 - 15	3(60.0%)	2(40.0%)	5(100%)			
16 - 25	1(100.0%)		1(100%)	3(100.0%)		3(100%)
26 - 35	15(71.4%)	6(28.6%)	21(100%)	8(66.7%)	4(33.3%)	12(100%)
36 - 45	30(50.8%)	29(49.2%)	59(100%)	21(40.4%)	31(59.6%)	52(100%)
Total	49(39.2%)	37(43.2%)	86(68.8%)	32(47.7%)	35(52.2%)	67(53.6%)

Table 2: Prevalence rate of various types of thyroid function abnormality

Thyroid function Abnormality	Sex		n=250 Total
	Female	Male	
Hypothyroid	0	2(100.0%)	2(0.80%)
Hyperthyroid	0	1(100.0%)	1(0.40%)

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Sub clinical hypothyroid	24(61.5%)	15(38.5%)	39(15.60%)
Sub clinical hyperthyroid	1(100.0%)	0	1(0.40%)
Sick Euthyroid	26(60.5%)	17(39.5%)	43(17.20%)
Normal	56(34.1%)	108(65.9%)	164(100.0%)
Total	107(42.8%)	143(57.2%)	250(100.0%)

Table 3: Distribution of thyroid function abnormality with respect to treatment status

HAART therapy	Thyroid function abnormality					n=86 Total
	Hypothyroid	Hyperthyroid	Sub hypothyroid	Sub hyperthyroid	Euthyroid	
Yes	2(3.92%)	1(1.96%)	23(45.10%)	1(1.96%)	24(55.8%)	51(59.3%)
No	-	-	16(45.71%)	-	19(54.29%)	35(40.7%)
Total	2(2.33%)	1(1.16%)	39(45.35%)	1(1.16%)	43(50.0%)	86(100.0%)

$\chi 2$ =0.083; d.f.=1; P=.773

Table 4: Distribution of thyroid function abnormality with respect to CD4 category

CD4 category	Thyroid function abnormality					n=86 Total
	Hypothyroid	Hyperthyroid	Sub clinical hypothyroid	Sub clinical hyperthyroid	Sick Euthyroid	
Category A	-	-	23(67.6%)	-	11(32.3%)	34(39.5%)
Category B	2(6.1%)	1(3.0%)	12(36.4%)	1(3.0%)	17(51.5%)	33(38.4%)
Category C	-	-	4(21.1%)	-	15(78.9%)	19(22.1%)
Total	2(2.33%)	1(1.16%)	39(45.35%)	1(1.16%)	43(50.0%)	86(100.0%)

$\chi 2$ =11.298; d.f.=2; P=.004

Table 5: Distribution of thyroid function abnormality with respect to CD4 category on HAART

CD4 category	HAART														
	Hypothyroid			Hyperthyroid			Sub clinical hypothyroid			Sub clinical hyperthyroid			Sick euthyroid		
	Female	Male	Total	Female	Male	Total	Female	Male	Total	Female	Male	Total	Female	Male	Total
Category A							7(58.3%)	5(41.7%)	12(100.0%)				4(40.0%)	6(60.0%)	10(100.0%)
Category B	0	2(100.0%)	2(100.0%)	0	1(100.0%)	1(100.0%)	4(50.0%)	4(50.0%)	8(100.0%)	1(100.0%)	0	1(100.0%)	3(75.0%)	1(25.0%)	4(100.0%)
Category C							1(33.3%)	2(66.7%)	3(100.0%)				8(80.0%)	2(20.0%)	10(100.0%)

Table 6: Distribution of thyroid function abnormality with respect to CD4 category without HAART

CD4 category	No HAART														
	Hypothyroid			Hyperthyroid			Sub clinical hypothyroid			Sub clinical hyperthyroid			Sick euthyroid		
	Female	Male	Total	Female	Male	Total	Female	Male	Total	Female	Male	Total	Female	Male	Total
Category A							11(100.0%)	0	11(100.0%)				0	1(100.0%)	1(100.0%)
Category B							1(25.0%)	3(75.0%)	4(100.0%)				8(61.5%)	5 (38.5%)	13(100.0%)
Category C							0	1(100.0%)	1(100.0%)				3(60.0%)	2 (40%)	5(100.0%)

Table-7 Correlation of HAART therapy and CD4 count with thyroid function abnormality

Spearman's rho (ρ)	HAART therapy	CD4 count
Thyroid function abnormality	.087	.304(**)

** Correlation is significant at the 0.01 level (2-tailed).

Patient on HAART therapy have higher percentage of thyroid function abnormalities 59.3%) versus 40.7%. Sick euthyroid (55.8%) and Sub clinical hypothyroid 45.10% being the commonest [Table 3]. HIV patients in Caterogy A has highest prevalence of thyroid dysfunction(39.5%), subclinical hypothyroid being the commonest [Table 4]. Patient on HAART, Thyroid dysfunction was common in Category A with the highest prevalence rate of subclinical hypothyroid [Table5]. Patients not on HAART, thyroid function abnormalities was common in category B with the highest prevalence of Sick euthyroid follow by subclinical hypothyroid [Table 6]. There was a positive correlation between thyroid function abnormality and HAART therapy but statistically not significant (ρ=0.087).Positive correlation exists between thyroid function abnormality and CD4 count but statistically insignificant ρ=0.304 [Table 7].

DISCUSSION

Thyroid dysfunction in HIV patients

In the present study, hyperthyroidism was seen in 1 (0.4%) patient and hypothyroidism in 2 (0.8%) patients which was comparable with studies by

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Meena LP et al.[12] Euthyroid state was seen in 164 (65.6%) patients, which was comparable with the study by Christopher et al.[7] The prevalence of thyroid dysfunction of 86 (34.4%) was comparable to previous reported studies, though the percentage of sub-types of thyroid dysfunction differ. In the present study sick Euthyroid 43 (17.2%) was commonest thyroid function abnormality followed by subclinical hypothyroidism 39 (15.6%). This is similar to the study by Madge et al,[11] where commonest abnormality was sick Euthyroid (17%) followed by subclinical hypothyroidism (4%). The major cause of these hormonal changes may be due to release of cytokines especially interlukin-6 and tumour necrosis factor (TNF). In the early stage of HIV infection T3 and T4 levels rise, T3 level fall with progression to AIDS, but TSH usually remains normal. Among HIV-infected populations, a high prevalence of non-thyroidal illness was reported among patients with terminal AIDS before the HAART era, with as many as 16% of patients. During severe illness, including advanced AIDS, 5-deiodination of T4 declines, leading to decreased T3 production and reverse T3 metabolism, and 5-deiodination of T4 to inactive reverse T3 is increased, creating a pattern of thyroid testing that suggests thyroid dysfunction.[7] This pattern, however, is a result of the physiological response to illness and not a result of abnormal thyroid function. And chronic HIV infection itself can lead to non-thyroidal illness because of changes in the peripheral thyroid hormonal metabolism related to the nutritional status.In a large cohort of HIV positive subjects followed for 3 years, Madge et al,[11] found the prevalence of hypothyroidism to be 2.5% (overt) and 4% (sub clinical). Hyperthyroidism (overt and sub clinical) occurred in <1% of patients. Non-thyroidal illness was seen in (17%) of patients whereas (75.5%) had normal thyroid function test. Only eight new cases (1%) of overt thyroid disease occurred over 3 years. They made a strong case against screening in HIV positive subjects.

Thyroid dysfunction on HAART therapy and without HAART therapy

In the present study, 51 (59.3%) of patients on HAART had thyroid function abnormalities compared to 35 (40.7%) of patients who were not on HAART. Among those who received HAART there were 2 (3.92%) hypothyroid, 1 (1.96%) hyperthyroid and 1 (1.96%) sub clinical hyperthyroid and this might be due to very less study subjects pertaining to those abnormalities as they had only 2, 1 and 1 cases respectively. On the other hand, among those receiving HAART, sick Euthyroid was the commonest thyroid function abnormality in 24 (55.8%) which was followed by Subclinical hypothyroid in 23 (45.10%), Hypothyroid in 2 (3.92%) and Hyperthyroid and Subclinical hyperthyroid in1 (1.96%) each. This pattern of thyroid dysfunction was similar to that seen in patients who were not on HAART where sick Euthyroid was seen in 19 (54.29%) and sub hypothyroid in 16 (41%) respectively. Nevertheless, a higher prevalence of subclinical hypothyroid and sick Euthyroid was seen among those who received HAART compared to those who don't receive HAART. In this study the association between thyroid dysfunction and treatment status is statistically insignificant (p=0.773). From this it might be concluded that there was no association between thyroid dysfunction in HIV infected patients with or without HAART. In the general population, the prevalence of subclinical hypothyroidism is 4.3%. Fifty to eighty percent (50-80%) of these individual have anti-thyroid peroxidase antibodies.[14,15] Subclinical hypothyroidism is common among HIV infected persons, especially among those who are receiving HAART, (prevalence, 3.5-12.2%).[13,16] However among patients with HIV infections and sub-clinical hypothyroidism, anti-thyroid peroxides antibodies are rarely identified, suggesting that the aetiology may not be autoimmune. Medge et al,[11] suggested a close relationship between serum thyroid hormone levels and nutritional status in HIV infected patients. There is decreased level of FT3 in poorly nourished HIV patients, called as euthyroid sick syndrome. This is the most probable mechanism for decreased FT3 in HIV patients.

Thyroid dysfunction in different categorises depending on CD4 count

In category A with a CD4 count below 200/mm3, there was 34 (39.5%) patients comparable with studies by Meena LP et al,[12] (33.3%) and Palaniswamy et al,[1] (34%). In category B with CD4 count between 200-350/mm3 there was 33 (38%) patients comparable with studies by Palaniswamy et al,[1] (46%) and Gagan Jain et al,[6] (42%). Lastly in category C with CD4 count above 350/mm3 there was 19 (23.2%) patients comparable. In this study there was a strong association between thyroid function abnormality and CD4 count (p=0.004). In the category B all the types of thyroid dysfunction was more common. Regarding subclinical hypothyroid, category A had the highest prevalence and category B became next to highest and category C had the least. Subclinical hypothyroidism was common in category A with HAART, and sick Euthyroid in category B without HAART. Thus there was a trend toward positive correlation between thyroid function abnormality and HAART therapy but the relationship is not significant enough statistically (p=0.087). On the contrary, there was a strong positive correlation between thyroid function abnormality and CD4 count (p=0.304). Thus it might be inferred that thyroid function abnormality had certain link with the CD4 level, where CD4 count declines with advancing HIV infection. Bordoux et al,[18] found that thyroid binding globulin was increased in 16 out of 54 HIV infected patients and correlated inversely with CD4 counts. A high prevalence of abnormalities in thyroid function tests was reported in previous cross-sectional studies. Unique abnormalities of thyroid function tests were reported by Lambert et al.[17] They described a

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progressive elevation in serum thyroxin binding globulin (TBG) but not in other binding proteins such as cortisol binding globulin (CBG) that accompanies a decline in CD4+ count with advancing HIV infection. Feldt-Rasmussen et al,[5] reported elevation of TSH and TBG concentration in conjunction with low FT-4 that occurs frequently and correlates with CD4+ cell depletion in AIDS patients. In addition this thyroid dysfunction correlated with the degree of immunosuppression and viral replication and preceded the worsening of the disease.

CONCLUSION

Thyroid function abnormalities are common in HIV patients with HAART or without HAART therapy. Sick Euthyroid is the commonest thyroid function abnormality followed by subclinical hypothyroidism.There is a direct correlation between low CD4 count with thyroid function abnormalities.In HIV patients with low CD4 count, screening for thyroid function abnormalities can be considered.The present study shows that thyroid dysfunction is frequent in HIV infection and with progression of disease there is a subclinical hypothyroid like stage that occurs in patients with advancing HIV infection. Various thyroid function tests such as FT3 /FT4 /serum TSH can be used as a surrogate marker as these correlate with the progression of the disease. The present study may not be giving the true picture of thyroid abnormality in HIV-AIDS as structural correlates of thyroid dysfunction could not be done in patients with hypothyroid like state. Beside this, serum reverse-tri-iodothyronine, serum thyroxin binding globulin levels and Thyrotropin Releasing Hormone (TRH) stimulation test could also not be done because of non-availability of these tests in our set up.

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