ORIGINAL ARTICLE

JIACM 2020; 21(3-4): 106-10

Prevalence and Predictors of Thyroid Dysfunction in Human Immunodeficiency Virus (HIV)-Infected Individuals

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Abstract

Introduction: Acquired immunodeficiency syndrome (AIDS) is a chronic multisystem disease also affecting the neuroendocrine system including thyroidal endocrine axis.

Methods: It was a cross-sectional, observational study, done in 100 HIV-infected individuals. The cases were divided into sub group A (50 patients on anti retroviral therapy (ART)) and sub group B (50 treatment naïve patients not on ART). 50 age and sex matched healthy controls were also recruited.

Results: Amongst 100 cases the overall prevalence of thyroid dysfunction was 45% [70% in sub group A versus 20% in sub group B ($p < 0.001$)] as compared to 9.4% in controls. Overt hypothyroidism was found in 10% cases [14% in group A vs 6% in group B ($p < 0.05$)]. Subclinical hypothyroidism (SCH) was the most prevalent condition seen in 30% of our cases [50% in group A and 10% in group B ($p < 0.0001$)] and 6% of controls. The mean TSH was significantly higher in cases as compared to controls (5.12 ± 1.80 µIU/L vs 3.81 ± 1.12 µIU/L) ($P < 0.001$) and in gp A as compared to gp B (5.81 ± 1.75 µIU/L vs 4.42 ± 1.59 µIU/L) ($P < 0.005$). Similarly FT_3 and FT_4 were significantly lower in cases as compared to controls ($P < 0.001$) and in gp A as compared to gp B ($P < 0.01$). Stepwise linear regression revealed HIV infection per se along with longer duration of disease, low CD4 cell counts, exposure to ART, longer duration of ART, male sex and past history of tuberculosis as strongest predictors of thyroid dysfunction in HIV-infected these individuals.

Conclusion: Thyroid disorders (specially subclinical hypothyroidism) is a very common but under-reported entity in patients with HIV/AIDS and virus per se along with ART seems to be the biggest factor affecting thyroid endocrinopathy.

Keywords: CD4count, HIV, subclinical hypothyroidism.

Introduction

Acquired immunodeficiency syndrome (AIDS) is a chronic multisystem disease and neuroendocrine system is no exception to that. Endocrine changes in the form of thyroidal, adrenal, gonadal, bone, and metabolic dysfunctions have all been reported in both early and late stages of HIV infection[1]. Alterations in endocrine function may be due to the possible relationship between the immune and endocrine systems, direct involvement of the gland by virus itself, secondary endocrine dysfunction due to indirect effect of cytokines, opportunistic infections or highly active anti-retroviral therapy (HAART)[2]. In the last two decades, the advent of potent and efficacious HAART has given rise to increased life expectancy and hence higher incidence of chronic diseases including endocrinopathies in HIV-infected individuals[3].

Amongst all endocrinopathies in people with HIV/AIDS, thyroid dysfunction is probably the commonest but least reported and various studies have reported it to be in the range of 10 - 15% out of which 1 - 2% manifest overt thyroid disease and subclinical thyroid disordershave been reported in 10 - 14%[4]. The association between thyroid abnormalities and HIV is well documented in western literature. However, there is a paucity of data regarding the same in Indian HIV-infected population which makes it difficult to make general recommendations about hormone testing and replacement therapy in these individuals. Apart from that, even though studies have reported a very high prevalence of thyroid abnormalities like subclinical hypothyroidism in individuals with HIV/AIDS but whether it is due to HIV itself or due to HAART is still not clear. This cross-sectional observational study was undertaken to determine the prevalence and the pattern of thyroid abnormalities in HIV-infected individuals and their association with various disease AIDS related factors including duration and type of antiretroviral therapy and level of immunodeficiency, i.e., CD4 cell counts.

Material and methods

It was a cross-sectional observational study done over a span of one year in the department of medicine and

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antiretroviral therapy (ART) centre at PGIMER, Dr RML Hospital after approval from the institutional ethical committee. The cases were 100 HIV-infected individuals, out of which 50 were on HAART (subgroup A) and 50 were HAART naïve, i.e., not on any anti-retroviral therapy (subgroup B). 50 age and sex-matched healthy relatives of cases volunteers were recruited as controls.

All cases with history of medical or surgical thyroid-related disorders (including use of thyroid hormones) any time in the past or with history of intake of drugs known to affect thyroid physiology, e.g., amiodarone, lithium, PAS, iodine, etc., were excluded. Similarly, all cases with past history of any opportunistic infections within the last one year or pre-existing cardiac, renal, or liver related disorder or delivery/ lactation within the last six months was also excluded.

A thorough history and physical examination including that of the thyroid glands was done. After an overnight fasting 10 ml venous blood sample was collected for estimation of routine baseline investigations and thyroid function tests including FT3/FT4/TSH and anti-TPO antibody levels. Chemiluminescent Enzyme Immunoassay (CLEIA) using VITROS immunodiagnostic kit was used for estimation of FT3, FT4 and anti-TPO levels. Felikrimunometric immunoassay technique was used to measure serum TSH levels.

BECTON-DICKINSON FACS flow cytometer was used to obtain CD4-cell counts.

The standard normal values of the thyroid function tests were taken as per the reference range in the department of biochemistry of our institution.

Thyroid stimulating hormone (TSH): 0.5 - 5.0 mIu/ml

Free T3 (FT3): 2.0 - 4.4 pg/ml

Free T4 (FT4): 0.7 - 2.0 ng/dl

Anti-thyroid peroxidase antibody (ANTI-TPOAb): Up to 50 IU/ml.

Definitions used in the study

- Overt hypothyroidism: raised TSH (> 10 mIu/ml) and low FT4 levels.
- Subclinical hypothyroidism: raised TSH (5.0 - 10 mIu/ml) and normal FT4 or FT3 levels.
- Overt hyperthyroidism: low TSH (< 0.5 mIu/ml) and raised levels of FT4 or FT3
- Subclinical hyperthyroidism: low TSH (< 0.5 mIu/ml) and normal FT4 or FT3 levels.
- Isolated low FT4: low FT4 levels with normal TSH and FT3 levels.

Statistical analysis

The analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0. Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non parametric tests were used.

Quantitative variables were compared using Independent T test/Mann Whitney test (for non-parametric data) to compare between cases and controls. Qualitative variables were compared using Chi-Square test/Fisher's exact test. Pearson correlation co-efficient was used to find out the association between thyroid function tests withthe duration of disease and HAART. P value of < 0.05 was considered statistically significant.

Results

A total of 100 HIV-infected individuals (cases) and 50 age and sex-matched healthy volunteers (controls) were enrolled in the study. The cases were further subdivided into subgroup A (50 cases on HAART) and subgroup B (50 cases not on HAART, i.e., treatment naïve). All subjects in subgroup A were on a combination of Tenofovir, Lamivudine and Efavirenz for at least two years. Amongst all subjects 60% were males and 30% were females. Maximum numbers of subjects (36%) were between 21 - 30 years of age group. The most common mode of transmission amongst all cases was heterosexual (77%) followed by homosexuality (3%), blood transfusion (4%), IV drug abuse (6%), and no cause was found in 10% of individuals and routine laboratory measurement were comparable amongst cases and controls.

Three out of every four cases complained of symptoms of easy fatiguability, lethargy, dry skin, irritability, and cold sensitivity; and females were significantly more symptomatic than males. However, sexual dysfunction was reported more by men (> 30%). None of the cases had clinically palpable goitre or any swelling in the neck or bruit. The mean CD4 cell counts of all the cases was 308.11/mm^3 [(292.44/mm^3 in subgroup A and 323.88/mm^3 in subgroup B). $p < 0.005$]. The profile of thyroid abnormalities in cases and controls was as under (Table I).

45% of cases as compared to 9.4% of controls had some thyroid dysfunction and the difference was statistically significant ($p < 0.001$). Similarly, overt or subclinical hypothyroidism was found significantly more in cases as compared to controls, i.e., 10% vs 3% and 30% vs 6% respectively. Similarly cases in subgroup A (cases on HAART) had significantly higher prevalence of overt and subclinical

hypothyroidism as compared to cases in subgroup B (i.e., treatment naïve cases) (14% vs 6% and 50% vs 10% respectively) and the difference was statistically significant. The anti-TPO antibody was found to be positive in five cases in subgroup A (10%) and 7 cases in subgroup B (14%). Two cases in subgroup A with anti-TPO positivity were found to have overt hypothyroidism and rest three had normal thyroid profile. The mean value of thyroid function tests amongst cases and controls has been tabulated in Table II.

Table I: Prevalence of thyroid abnormalities in cases (including subgroups) and controls.

	All Cases	Controls	Statistical difference	Subgroup A	Subgroup B	Statistical difference
Overall Thyroid dysfunctions	45%	9.4%	$p < 0.001$	70%	20%	$p < 0.05$
Overt hypothyroidism	10%	3%	$p < 0.005$	14%	6%	$p < 0.05$
Subclinical hypothyroidism	30%	6%	$p < 0.0001$	50%	10%	$p < 0.05$
Isolated low FT_4	5%	0.3%	$p < 0.05$	6%	4%	$p < 0.01$
Subclinical/overt hyperthyroidism	0%	0%		0%	0%	
Anti TPO positivity	12%	8.9%		10%	14%	

Table II: Profile of thyroid function test in cases (including subgroups) and controls.

Mean values	Cases (n = 100)	Controls (n = 50)	P value (cases vs controls)	Subgroup A (n = 50)	Subgroup B (n = 50)	P value (GP A vs GP B)
TSH (μIU/L)	5.12 ± 1.80	3.81 ± 1.12	< 0.001	5.81 ± 1.75	4.42 ± 1.59	< 0.001
FT_3 (pg/ml)	2.38 ± 0.63	3.37 ± 0.73	< 0.01	2.62 ± 0.74	2.86 ± 0.77	< 0.04
Mean FT_4 (ng/ml)	1.26 ± 0.48	1.45 ± 0.43	< 0.05	1.18 ± 0.36	1.34 ± 0.56	< 0.01
Mean Anti TPO (IU/ml)	26.44 ± 6.92	28.86 ± 7.48	< 0.11	24.78 ± 5.48	28.13 ± 6.58	< 0.09

The mean value of TSH amongst cases was significantly higher than in controls [5.12 mIU/ml vs 3.81 mIU/ml ($p < 0.001$)]. Likewise mean FT3 and FT4 levels were significantly lower in cases as compared to controls implying that infection with HIV itself is associated with higher TSH (released from pituitary) and lower FT3/FT4 levels. Similarly, mean TSH was significantly higher in subgroup A as compared to subgroup B and likewise levels of FT3/FT4 were lower in subgroup A as compared to subgroup B [5.81 vs 4.42 mIU/ml ($p < 0.001$)] implying that HAART by itself may have a significant impact on the levels of thyroid hormones. The levels of TSH were significantly higher and FT3/FT4 were significantly low in subgroup B as compared to controls meaning that HIV by itself (without the added impact of HAART) has a profound effect on the causation of hypothyroidism, meaning that HIV per se may have a direct suppressive effect on hormone production by thyroid gland (FT3 and FT4) and since FT3/FT4 have a feedback mechanism effect on the release of TSH from pituitary so there is a concomitant increase in the levels of TSH in these cases. Inspite of the so high prevalence of thyroid dysfunction and subclinical hypothyroidism reaching upto 45% and 30% respectively, only 12% of the cases had high anti TPO levels (10% in subgroup A and 14% in subgroup B), meaning that thyroid dysfunction in all cases and specially cases in subgroup A were more not because of immune phenomenon virus-induced thyroid destruction or effect of HAART itself on thyroid or pituitary.

Amongst cases in sub group A with thyroid dysfunction the mean duration of HAART therapy was 42.76 ± 11.23 months as compared to 36.77 ± 8.21 months in in those with normal thyroid functions ($p < 0.05$). It was found that there was a direct correlation between the duration of HAART and the levels of TSH ($r = 0.4748$, p value = 0.00051 within 95% confidence limit). There was an inverse correlation of duration of HAART with serum FT4 levels. ($r = 0.4575$, p value = 0.0008, within 95% confidence limit). Also it was seen that the levels of FT3 numerically decreased with the increase in the duration of HAART however, it could not reach statistical significance. ($r = 0.2692$, p value = 0.0587). The co-efficient of the linear regression also revealed that for every increase in HAART duration by 1 month, the levels of TSH would increase by 0.0304 mIU/L. On the contrary to the current literature, more percentage of males than females had thyroid dysfunction and none had high anti-TPO levels. No correlation was found between thyroid dysfunction and any particular class of drug used in HAART.

The cases in subgroup A had significantly higher TSH and significantly lower FT3/FT4 and anti TPO as compared to subgroup B ($p < 0.001$). Stepwise linear regression revealed that HIV infection per se along with longer duration of HIV infection, lower CD4 cell counts, exposure to HAART by itself along with longer duration of HAART, male sex, and past history of tuberculosis were strongest predictors of clinical or subclinical thyroid dysfunction in patients with HIV/AIDS. However, multiple regression analysis revealed that infection by HIV per se along with severity of immune suppression (i.e., CD4 cell counts) and treatment with highly active antiretroviral therapy (HAART) were the major predictors of thyroid dysfunction in these HIV-infected individuals.

Discussion

According to literature, overt or subclinical thyroid

dysfunction occurs at almost similar or slightly increased rates in HIV-infected individuals as compared to the general population[5]. Moreover, HAART therapy can complicate thyroid functions further through drug interactions and the immune reconstitution inflammatory syndrome[6]. However, contrary to the existing literature our study found that thyroid dysfunction is rampant in people living with HIV/AIDS and occurs much more frequently in patients receiving HAART. Mean TSH levels were significantly higher in our cases as compared to controls (5.12 vs 3.81 mIu/ml). Even the cases in subgroup B had significantly higher mean TSH and levels FT3/FT4 as compared to controls meaning that HIV seems to be the major culprit behind causation of hypothyroidism (clinical or subclinical) in HIV-infected individuals.

A similar study by Jain *et al*[7] in 2009 showed higher TSH values(4.135 ± 3.231 mIU/ml) in HIV positive patients as compared to healthy controls. Similarly, higher TSH values were also obtained in HIV-infected individuals by Olivieri *et al*[8]. The overall mean value of TSH obtained was 4.8 ± 2.7 mIu/ml. This finding was contrary to findings by, Lopresti *et al*[9] where they could not find any increase in TSH levels as compared to controls. The reason behind higher TSH in HIV-infected individuals in our study as compared to other studies was that the mean duration of disease in our study cases was more than five years as compared to two years in other studies. This may have led to more exposure and hence destruction/injury to thyroid gland by viral particles, inflammatory cells and opportunistic infections and hence the injured thyroid gland could not produce enough thyroid hormone leading to higher TSH (by feedback mechanism). The most prevalent thyroid abnormality in our study was subclinical hypothyroidism, prevalence being 30% amongst cases. It was significantly higher when compared with various other studies being reported as 3.5% by Collazos *et al* in 2003[10], 6% by Ketsamathi *et al* in 2006[11], 4% by Madge *et al* in 2006[12] and 10.6% by Bongiovani *et al* in 2006[13]. The only study having similar prevalence as our study was by Meena *et al*[14] from India in 2011 who also reported a 30% prevalence of subclinical hypothyroidism in HIV positive individuals. It was observed in our study that the prevalence of subclinical hypothyroidism amongst cases on anti-retroviral therapy was 50% as compared to only 10% in cases not on any antiretroviral therapy. This higher prevalence in subgroup A suggests a definite role of antiretroviral drugs in the derangement of thyroid functions as proposed by Bongiovani *et al*[13] and Grappin *et al*[15]. Apart from some probable toxicity by HAART to thyroid gland, immune reconstitution syndrome (IRS) could have also led to thyroid injury. Amongst commonest IRS entities, thyroiditis is quite common, the manifestations of which are mostly mild and subclinical. Apart from that, other nutritional and metabolic deficiencies like hypoproteinaemia (which are common in Indian HIV-infected individuals) could have added to that. Apart from that we could find that anti-TPO antibody levels (and hence thyroiditis) is not a major cause of hypothyroidism in people with HIV/AIDS (contrary to general population) and HIV-related factors majorly affect thyroid endocrinopathy in these individuals.

Hence, the current study also consolidates the fact that much higher prevalence rate with predominant sub-clinical hypothyroidism is found in Indian HIV positive individuals. The study also revealed strong direct correlation between hypothyroidism (clinical or subclinical) and disease severity (i.e., low CD4 cells count), longer duration of HIV infection along with HAART by itself and longer duration of HAART. The linear regression analysis further strengthened the relationship between the worsening of thyroid function tests culminating into subclinical hypothyroidism and these disease parameters. Hence, there lies a future possibility of early use of thyroid function tests and thyroxine replacement as a tool to manage AIDS along with co-morbidities like metabolic syndrome, central obesity, myopathy, depression, osteoporosis, etc., (where subclinical hypothyroidism has been seen to be associated with these pathologies) in HIV-infected individuals.

Surprisingly, males in our study had higher burden of thyroid abnormalities as compared to females and can be explained by the fact that access to health care and ART is significantly earlier and easier for males than females in India. That could have resulted into earlier initiation and hence longer duration of HAART in males, and hence more of thyroid abnormalities.

Our study recapitulates the significance of regular monitoring of thyroid function tests in HIV-infected individuals and more so when they are on highly active anti-retroviral therapy. However, it is still controversial whether the subclinical hypothyroidism in these individuals should be treated or not, with no current guidelines for the same (at least in people with HIV/AIDS).

Limitations

Our study had majority of HIV-infected individuals in intermediate-to-advanced immune deficiency state with mean CD4 cell counts of 308.16/μl. The higher prevalence of thyroid dysfunction in the study population might be due to the lower CD4 cell counts in subjects. Apart from that, the patients were taken from the ART centre, half of whom were on pre-treatment with combination of three anti-retroviral drugs so the role of single antiretroviral drugs could not be evaluated in the study. Viral load testing was not done and hence the correlation of abnormal TFT with disease severity by measurement of CD4 cell counts

(immunological failure) cannot be extrapolated to virological failure (by viral load testing). Further larger prospective studies with higher number of HIV positive individuals may be the need of the hour to better assess the clinical impact of subclinical hypothyroidism in HIV-infected subjects.

Conclusion

Thyroid disorders (especially subclinical hypothyroidism) is a very common but under-reported entity in patients with HIV/AIDS and HIV virus per se along with ART seems to be the biggest factor affecting thyroid endocrinopathy.

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