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Thyroid Status Among HIV Infected Cases Attending ART Centre JNIMS And Correlation Between TSH(US) And CD4Count

Suchitra Chongtham[1], Narmada Thongam[2], LamabamChanchan Chanu[3], Rosyka Laithangbam[4], Sujeeta Oinam[5], KhLokeshwar Singh[6]
[1]*Associate Professor, Department of Biochemistry, JNIMS, Manipur, India*
[2]*Assistant Professor, Department of Biochemistry, JNIMS, Manipur, India*
[3]*Assistant Professor, Department of Biochemistry, JNIMS, Manipur, India*
[4]*PGT, Department of Biochemistry, JNIMS, Manipur, India*
[5]*PGT, Department of Biochemistry, JNIMS, Manipur, India*
[6]*Associate Professor, Department of Medicine, JNIMS, Manipur, India*
**Correspondence:Dr. Narmada Thongam*

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I. Introduction

There is some evidence to suggest an increasing number of patients taking ART drugs are presenting with thyroid disorders.Thyroid hormone plays a fundamental role in metabolism and regulate immune system[1].HIV infection involves almost all the organs and systems including endocrine glands.So an alteration in the thyroid function is possible if not directly by the virus itself[2,3].Specific pattern of abnormal TFT findings are more frequently identified among HIV infected patients although the prevalence of overt thyroid disease does not appear to be significantly increased in HIV infected patients compared with general population.[4]Discrepency remains in the prevalence rate of thyroid dysfunction reported from India and abroad.There is still a lack of a concrete evidence of thyroid dysfunction in patients on ART and also with the duration of the disease.Owing to the paucity of data of thyroid study in HIV cases on ART, this study was conducted in northeastern part of the country with an objective to find out the thyroid status among HIV positive cases attending ART centre JNIMS and also to find out correlation,ifany,betweenultrasensitive TSH(usTSH) and CD4 count.

II. Materials and methods

This cross sectional study was conducted at ART Centre JNIMS Hospital,a tertiary care centre at Imphal,Manipuron a cohort of 191 confirmed HIV positive cases in the age group18yearsandabove,irrespective of sex ,caste, creed or religion.EligibleHIV confirmed cases attending ART centreJNIMS were randomly selected and enrolled for the study during the period between March 2015-September 2015 after taking written informed consent.

A detailed clinical history of the covariates including route of infection, duration from the time of diagnosis of HIV,duration on ART drug intake,any untoward incident, drugs reaction etc.wasrecorded,along with which a detailed clinical examination was done in each subject.

Exclusion criteria: Acutely ill,HepatitisB,C coinfections,pregnantwomen,Diabetes mellitus, cases with previous history of thyroid dysfunction or drug intake were excluded from the study.

Ethical statement : Ethical clearance from institutional ethical committee,JNIMS was obtained prior to the onset of the study.

After taking due informed consent 5 ml of fasting venous blood was collected from ante-cubital vein after taking aseptic and antiseptic precautions between 8-10 AM.Out of the total blood volume collected 2.5 ml was separated in K_2EDTAvaccutainer and sent for CD4 count.Serum was separated later from the remaining 2.5 ml and thyroid hormones$freeT_3$(fT_3),$freeT_4$(fT_4) and ultrasensitive usTSH were analysed on the same day.

Thyroid function was assessed by measuring serum free T_3(fT3),$freeT_4$(fT4), andultra sensitive TSH(usTSH) by quantitative ELISA method using Benesphera and DRG kits in Biochemistry Department JNIMS. As per the manufacturer's protocol the normal ranges of usTSH,fT3 and fT4 were (0.54- 4.72) µIU/ml,(1.4 -4.2) pg/ml and (0.8-2.0) µg/dl respectively.Thyroid disorders were categorized as

hyperthyroidism(overproduction of T3 and T4) and hypothyroidism (underproduction of T3,and T4).Hypothyroidism was further categorized as overt (high TSH,low T4) and subclinical (high TSH,normal T4)and low ft4 (normal TSH and fT4<1.4 pg/ml).Similarly hyperthyroidism was categorized as subclinical (TSH<- 0.3 µIU/ml, normal fT4) and overt hyperthyroidism(TSH<- 0.3 µIU/ml,fT4>4.2 pg/ml).This classification is based as per the report published by Beltran S et al.[5]

Other routine test parameters like Serum Alanine transaminase(ALT) and Aspartate transaminase(AST) were measured with kinetic method with pyridoxal-5 phosphate(LDH/NADH)and pyridoxal-5phosphate(visible method) respectively,in Vitros-250 dry chemistry autoanalyzer.Blood urea was determined by urease with indicator dye method, serum creatinine by enzymatic(creatinineamiohydrolase) method in the same machine

Blood CD4 count was done by flow cytometry, Beckton Dickenson fluorescent activated cell sorter (FACS) machine in Microbiology Department,JNIMS.Hemoglogin was done in automated hematological counter in Pathology department.

III. Results

A total of 191 retro reactive patients on Anti Retro Viral Therapy (ART), attending ART Centre JNIMS were selected in a random manner.The data collected was fitted into microsoft excel format and analysed using SPSS version 21.

The study parameters were expressed as mean ±SD,median, percentage(%).Karl Pearson's correlation test was applied to find correlation (r) between the clinical parameters and the statistical significance level of the tests was taken at Probability value $P < 0.05$.

Out of the total study group majority120 (62.8%) were females and 71(37.2%) were males and most of them were married.The average age of the subjects was 40(±8.8) with a median age of 40 years .Mean weight of the subjects was 53.5±8.1 kg with a maximum of 71 kg and minimum of 27 kg ,Mean Hemoglobin was12.1 (1.4)gm%.The average CD4 count level was446.2(207.9)/cumm ranging from 42/mm³ to 1110/ mm³ .

Serum ALT and AST were 49.1(31.1)U/l and 43.5(33.8)U/l respectively. Average blood urea and creatinine levels were 2.8(7.1) mg/dl and 0.91(1.4) mg/dl respectively.

Thyroid hormones fT3,fT4, and usTSH assays measured an average of 2.19(0.55)pg/ml,1.24(0.32) µg/dl and 2.1(1.75) µIU/ml respectively.

Variable	Parameter Mean±SD	Median	Minimum	Maximum
Weight (Kg)	53.3±8.1	54	27	71
Hb (gm%)	12.1(1.4)	12	7	16
CD4 (per cumm)	446.2(207.9)	443	42	1110
AST(U/L)	43.5(33.8)	35	10	282
ALT(U/L)	49.1(31.1)	42	13	260
Urea(mg/dl)	22.8(7.1)	22	1	78
Creatinine (mg/dl)	0.91(1.4)	0.8	0	21
fT3(pg/ml)	2.19(0.55)	2.1	0.8	4.0
fT4(µg/dl)	1.24(0.32)	1.2	0.0	2.8
usTSH(µIU/ml)	2.10(1.75)	1.6	0.2	8.1
Duration (yr)	5.94(2.75)	6.3	0	11.0

Table1: Showing Mean(SD) of recorded variables of the cases (N=191)

Out of 191 subjects majority 165(86.4%) were euthyroid. Among the thyroid dysfunctions 17 (8.9%) were subclinical hypothyroid with only 2(1%) overt hypothyroid cases.There were 5 (2.6%) subclinical hyperthyroid cases and 2(1.0%) overtly hyperthyroid cases.

Thyroid profile	Number	Percentage (%)
Normal	165	86.4
Subhypo	17	8.9
Hypo	2	1.0
Subhyper	5	2.6
Hyper	2	1.0

Table 2: distribution of subjects according to their thyroid status

When Karl Pearson's correlation test was applied between CD4 and clinical parameters a significant negative correlation was shown between CD4 and ALT ($r = - 0.154$) with(P value $= 0.033$)but correlation between CD4 and AST($r= - 0.120$) was not significant($r = - 0.099$); CD4 and blood urea ($r= - 0.159$); ($P = 0.028$)whereas a positive correlation was observed between CD4 and Hb ($r = 0.177$) with a P value = 0.015 which is significant

Parameters	Number	Pearson's correlation coefficient (r)	p-value
fT3 (pg/ml)	191	0.001	0.991
fT4 (µg/dl)	191	0.012	0.868
usTSH (µIU/ml)	191	0.052	0.479
AST (U/L)	191	-0.120	0.099
ALT(U/L)	191	-0.154	0.033*
Urea mg/dl	191	-0.159	0.028*
Creatininemg/dl	191	-0.133	0.066
Hb(gm%)	191	0.177	0.015*

Table 3: Pearson's Correlation test between clinical parameters with CD4 level

Parameters	Number	Pearson's correlation coefficient (r)	p-value
fT3	191	-0.002	0.975
fT4	191	0.121	0.095
usTSH	191	0.059	0.414
CD4	191	0.137	0.059
AST	191	0.038	0.600
ALT	191	0.034	0.643
Urea	191	-0.071	0.327
Creatinine	191	0.110	0.130
Hb(gm%)	191	0.112	0.123

Table 4: Pearson's Correlation between clinical parameters with duration of treatment (years)

On an average the subjects in the study group were on ART for 5.94(2.75) years (Table.4). A negative correlation (r = -0.002) was observed between fT3 and duration (years) of treatment with ART.Blood urea levelalso had a negative correlation (r= - 0.071) with the duration of therapy. In both the cases statistical significance was not detected P > 0.05.

Whereas minimal positive correlation was seen between fT4,usTSH,CD4,ALT,AST,Creatinine and Hb with the duration on ART they were all statistically insignificant with P>0.05

IV. Discussion

The subjects in the study had been on ART for varying period of time including those who had taken for only fewmonths.There was a female predominance reflecting transmission from their spouse.The CD4 count of most cases were in the range(401-500)/mm³ and were clinically stable and asymptomatic

HIV infection may cause adaptive changes in thyroid functions and often do not require treatment.Non specific signs and symptoms of thyroid dysfunction may overlap with non endocrine disorders which are common in HIV infected patients.Moreover some medications used to treat HIV infection and its complications can induce thyroid dysfunction.[6]

The female predominance in the study group could be a reflection of onward transmission from their male counterpart.The high mean age 40(+ - 8.8) years of the subjects may be due to HAART increasing the longivity of survival.The average CD4 count of the subjects was 446.2(207.9)/mm³ with a median value of 443mm³ ,most of them being clinically stable and asymptomatic.

In our study out of 191 cases only 13.5 % of them had thyroid dysfunction.Within this group subclinical hypothyroidism existed in 17(8.9 %) cases and overt hypothyroidism prevailed in just 2(1%) cases.Whereas 5(2.5 %) cases of subclinical hyperthyroid were detected only 2(1%) cases were overtly hyperthyroid.

This prevalence findingofsubclinical hypothyroidism closely tallies with that of Rajendra Kumar et.al[7] with 12% subclinical hypothyroid cases although their number of overt hypothyroidism (6%) outnumbered that in our study (1%).The overall thyroid dysfunction in our study was (13.5%) as compared to theirs with (20%).According to Madeddu G et al[8] thyroid abnormalities, mostly subclinical hypothyroidism were associated with HAART therapy particularly Stavudine. Our findings are also comparable to that of Beltran et.al[5] with 16% cases out of 350 HIV patients having subclinical hypothyroidism and (2.6%) overt hypothyroidism. Similar figure was observed by Sharma et al[9] where (14.76%) out of 359 HIV cases were hypothyroid and (5.29%) were having sick euthyroid syndrome.

In contrast to these a much higher and alarming figure was found in a study by Dev N et al where the prevalence of thyroid dysfunction was 75.5% of which 53% were having subclinical hypothyroidism. In a Spanish study by Collazos et al[11] (3.5%) had subclinical hypothyroidism which correlated with low CD4 count but no significant correlation was found between hypothyroidism and CD4 in our study.There was (2.6%) subclinical hyperthyroid but only (1%) overt hyperthyroid cases.This is in near agreement with findings of Madge et.al[12] with(<1%) hyperthyroid case .

In our study there was negligible correlation observed between CD4 count and thyroid hormones fT3,fT4,usTSH which were statistically insignificant. A similar observation was made by Surjit Kumar Tripathy et.al.[13] Contrary to this statement**,** Meena LP et.al[14]found an elevation of TSH when CD4 cunt was <200/cumm.

Jain G et.al[15] reported that abnormal thyroid level correlated with CD4 count and severity of disease.Another studyby Collazos[11] also found a low fT4 level (1.3%) and subclinical hypothyroidism (3.5%) which correlated with low CD4 count.

A negative correlation was found between CD4 count and ALT and AST but significance was found only with ALT.A tendency of ALT to increase with lowering of CD4 was seen . A similar observation of higher liver enzyme abnormalityin both ART experienced and ART naïve HIV-1 infected patients was made by Melashu et.al.[16]Based on the grading of hepatotoxicity[17]only 10.5 % of our subjects on ART had grade I hepatotoxicity (AST,ALT level>1.25-2.5 X UNL) and 4.1 % were having grade II hepatotoxicity(2.6-5 X UNL) and none of them had severe grades as most of them were clinically stable. The prevalence of liver enzyme abnormalities in this study was 14.6% when compared to(20%) in other studies by Melashu BS et al[16], Cameroon((22.6%)[18],South Africa (23%)[19],brazil(19.7%)[20] .However the prevalence was lower in (11%) in the general population of Australia.[17].

As the duration on ART increases serum ALT,AST tend to rise.The elevated liver enzymes in HIV infected patients might be due to inflammation of hepatocytes by HIV through apoptosis,mitochondrial dysfunction and permeability alteration in mitochondrial membrane that stimulates an inflammatory response [21][22] [23] [24].Adverse drug reactions due to HAART are common ranging from mild to life threatening conditions.They usually occur within first 6-12 weeks but metabolic toxicities happen following prolonged use of antiretroviral therapy.

The observed negative correlation between blood urea and duration on ART could be a slight reflection of lowering metabolic activity of liver in synthesizing urea but a coexisting kidney dysfunction could be ruled out by serum creatinine level and other early markers in suspicious cases.

V. Conclusion

Although thyroid dysfunction is believed to be more common among HIV-infected patients on ART ,in our study we found negligible correlation between CD4 count and thyroid hormones fT3,fT4 and usTSH. It was also found that thyroid dysfunctionhad poor correlation with duration of ARTeven though thyroid hormone abnormalities, predominantly subclinical hypothyroidism were encountered in some cases of the study population.Serum liver enzymes ALT,AST,blood urea ,creatinine,Hb levels need to be regularly checked in patients on ART.In spite of the above findings,thyroid function testing from time to time cannot be overlooked until it is substantiated by a well designedlongitudinal study on a larger sample size.

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