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ORIGINAL ARTICLE

Serum Levels of Thyroid Hormones in Relapsing Remitting Multiple Sclerosis

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ABSTRACT

Background: Multiple sclerosis is a neurologic disorder characterized by recurrent episodes of demyelination and axonal injury. Myelin sheath destruction is associated with loss of oligodendrocytes responsible for creating and maintaining it. This leads to decrease conduction of action potential and damage even in early stages. Thyroid hormones (THs) play a critical role in the central nervous system (CNS) development, neuronal growth regulation and synaptogenesis. Any transient and moderate deficiency or excess of THs during critical periods of development or during adulthood can cause neurological abnormality, This study aimed at determination of serum thyroid hormones levels in patients with Relapsing Remitting Multiple Sclerosis (RRMS), and to explore relationship between these thyroid hormones and disease

Methods: A Case- control study was carried out on twenty five patients with clinically definite relapsing remitting multiple sclerosis (according to the Mc Donald criteria 2017**)** compared to twenty five healthy age and sex matched controls. We used the serum of the patients and the controls to measure the level of free triiodothyronine (FT3), free thyroxine (FT4), and thyrotropin (TSH) hormones using Automated Cobas e Immunoassay analyzers based on electrochemiluminescent technology that is the using of ruthenium complex and the measuring cell

Results: There was no statistically significant difference between the two studied groups in FT4 and TSH but there was a statistically significant increase in frequency of decreased FT3 among patients group. There was negative significant correlation between FT3 and Expanded Disability Status Scale (EDSS).

Conclusions: Our study demonstrates a decrease in the level of thyroid hormone (Free T3) among MS patients and a negative significant correlation between Free T3 and EDSS.

Keywords: Ft3 free triiodothyronine; Ft4 & free thyroxine; TSH thyrotropin ;

INTRODUCTION

Multiple Sclerosis is a neurologic disorder characterized by inflammation, demylination with a variable degree of diffuse axonal and neuronal degeneration throughout the central nervous system **[1].** It is so called as sclerosis refers to the scars (sclerae) that formed in the nervous system (also called plaques) and "Multiple" also indicates that its symptoms are dispersed in time and space **[2].** These lesions occur commonly in the white matter in optic nerve, basal ganglia, brain stem, spinal cord and around lateral ventricles **[3].** It has an enormous impact on quality of life and social costs due to lost work and cost of providing care **[4].** Thyroid hormones are important factors affecting MS progression. 3,30,50-triiodothyronine (T3) is the active form of TH in the body, which is transformed from 3,5,3,5-tetraiodothyronine (T4). It is widely believed that thyroid hormones are necessary for normal timing in the oligodendrocyte progenitor cells (OPCs) differentiation and maturation [**5].** It is also necessary for producing the myelin sheath [**6]**, arresting the cell cycle**[7]** and trans differentiation **[8].** In addition to its role in the differentiation and maturation of oligodendrocytes via nuclear hormone receptors, it also plays a role in the migration of OPCs in the subventricular zone (SVZ)**[9].** Thyroid hormones are important for CNS myelination and may be critical for remyelination **[10, 11].** It is well established that demyelination during MS increases active

astrocytes and the inflammation of microglia. This results in prevention of remyelination due to the formation of a barrier that blocks the proliferation and differentiation of oligodendrocytes **[12].** Treatment using T3 leads to a reduction in the number of active astrocytes induced by cuprizone(CPZ). A deficiency of T3, resulting from 6-propyl-2- thiouracil (PTU) administration, promotes an increase in the number of active astrocytes. So it is suggested that T3 inhibits active astrocytes to help remyelination ([**13**].

METHODS

This case- control study was carried out on twenty five patients with clinically definite relapsing remitting multiple sclerosis (according to the revised Mc Donald criteria 2017)**[14],** selected from Inpatient and Outpatient Clinic of Neurology Department, Zagazig University and Alahrar Teaching Hospitals in Zagazig in addition, and on twenty five healthy age and sex matched controls. Written informed consent was obtained from all participants and no harmful maneuvers were performed or used for any one. Institutional Review Board , faculty of medicine, Zagazig University has given approval . The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.Patients with relapsing remitting multiple sclerosis (RRMS)disease were classified as relapsing if there were appearance of new symptoms, or the return of old symptoms, for a period of 24 hours or more and occurred at least 30 days after the last relapse in the absence of a change in core body temperature or infection , and as remitting if patients were presented after a duration of one month from the clinical attack and when symptoms had become stable [**15].**

Inclusion criteria:

Patient with relapsing remittent multiple sclerosis who are diagnosed according to the revised McDonald criteria 2017 **[14]** and aged between 15 and 50 years old are included in the study.

Exclusion criteria:

We excluded patients with medical history of comorbidities (stroke, thyroid diseases, hepatic or renal dysfunctions, dementia), with acute medical conditions (infections and surgical interventions) in the three months before this study and with medical conditions such as heart failure and respiratory failure or drugs that may affect thyroid hormone levels. All patients were subjected to detailed history taking about age of onset, duration of disease, number of relapse and current treatment , to general examination with special attention on thyroid gland and vital signs especially blood pressure ,detailed neurological examination and assessment of disease severity by the Expanded Disability Status Scale (EDSS): Which is a scale used to quantify disability in eight function systems, pyramidal, cerebral, cerebellar, brain stem, sensory, visual, bowel and bladder and other functions was performed to the patients. Patients were categorized according to the severity of their disease into Mild (0-3) Moderate (3.5-5.5) Severe (6-9.5) **[16].**Brain and spinal MRI images were done in the MR unit of Zagazig University Hospitals and that of Alahrar Teaching Hospital in Zagazig for all the patients. All the MRI examinations were performed using Atchiva MRI scanner Philips (1.5 tesla) . The routine examination consisted of axial, sagittal and coronal slices. We used T1-Weighted images ,T2-Weigted images ,FLAIR Images (sagittal flare) and T1-Gadolinium enhancement images techniques . Positive MRI brain images were defined in concordance to criteria of Fazekas et al **[17]** as the appearance of three or more ellipsoid demyelinating lesions whose diameters were 3 mm or more within the brain. Of these lesions, at least one lesion was evident to be within the periventricular white matter or brain stem in a diameter of 6 mm or more. Patients with MS are considered as having MRI activity if they had one or more Gd enhancing lesions in T1-Weighted image **[18].** At Labs of Zagazig University and Alahrar Teaching Hospitals all patients were subjected to routine laboratory investigations as complete blood picture, liver function test, kidney function test and random blood sugar.

Blood samples from the patients and the controls were collected without using an anticoagulant , allowed to clot for 30 min. at 25°C ,Centrifuged at 3,000 or 3,500 rpm for 5 min .then the serum was transferred as much as possible into 5 ml polypropylene tube.

In vitro quantitative determination of free triiodothyronine, free thyroxine, and thyrotropin in human serum are performed using Automated Cobas e Immunoassay Analyzers based on electrochemiluminescent technology that is the using of ruthenium complex and the measuring cell.In the Elecsys FT3 test the determination of free triiodothyronine is made with the aid of a specific anti- T3 antibody labeled with a ruthenium complex.In the Elecsys FT4 test the determination of free thyroxine is made with the aid of a specific anti- T4 antibody labeled with a ruthenium complex.The quantity of antibody used is so small (equivalent to approx. 1-2 % of the total T4 content of a normal serum sample) that the equilibrium between bound and unbound T4 remains virtually unaffected. The Elecsys TSH assay employs monoclonal antibodies specifically directed against human TSH. The antibodies labeled with ruthenium complex consist of a chimeric construct from human and mouse- specific components.As a

result, interfering effects due to HAMA (human anti-mouse antibodies) are largely eliminated.

Free T3(3.1-6.8 pmol) :Free T4(12-22 pmol) ;TSH(0.3-4.2mIU/L) are normal ranges.

STATISTICAL ANALYSIS

The obtained data were tabulated and analyzed using Statistical Package of Social Science (SPSS version, 22) (Levesque, 2007)**.** Continuous variables were expressed as the mean ± SD (standard deviation) and median (range). In the independent samples, Independent -t test was used to compare two groups of normally distributed data while, Mann Whitney MW test was used for non-normally distributed data. One way ANOVA was used to compare more than two groups of normally distributed data. Percent of categorical variables were compared using the Chi-square test. Correlation coefficient (Spearman's or Pearson's) was calculated to assess the relations between serum level of MDA and thyroid hormones and clinical severity of MS using the Expanded Disability Status Scale (EDSS).

Level of significance: For all above mentioned statistical test done, the threshold of significance is fixed at 5% level (P value) [**19]**,P value of > 0.05 indicates non-significant results ,P value of ≤ 0.05 indicates significant results ,P value of <0.001 indicates highly significant results. The smaller the p value obtained the more significant are the results**.**

RESULTS

Twenty-five (25) patients with clinically definite relapsing remitting multiple sclerosis were enrolled for this study. We observed that ages of MS patients ranged from 19 years to 50 years with mean age of (37.4 ± 8.03) (Table 1).

In our present work (as in Table 2) we found that there were no statistical significance difference between the two studied groups in Free T4 and TSH but there was statistical significance decrease in frequency of Free T3 level among cases group.

Regarding correlation between Thyroid hormones levels and age, EDSS, No of T2 lesions, relapse, disease course and gadolenium enhancement in MRI among cases group which is presented in (Table 3,5) , there was a negative significant correlation between Free T3 and duration, EDSS, and number of relapse. Also there were –ve significant correlation between Free T4 and number of T2 lesions .

In (Table 4) there was a decrease in Free T3 among cases without medical treatment compared to treated cases with DMT (IFN-β1a) but there was no statistical significance differences in between them in free T4 and TSH level.

In (Table5) we found no statistical significance differences between free T3, T4 or TSH level and disease course and gadolenium enhancement in MRI among cases group.

Results of our study in (Table6) showed statistical significance decrease in FT3 in severe cases compared to mild and moderate cases. But there were no statistical significance differences in between them in free T4 or TSH level.

Table 1: Socio-demographic data of the two studied groups:

Variable	**Cases (n=25)**		**Control (n=25)**		**t**	**P**
Age : (year)						
Mean ± SD	37.4 ± 8.03		32.76 ± 10.25		1.78	0.08
Range	19 – 50		15 – 50			NS
Variable	**No**	**%**	**No**	**%**	χ^2	**P**
Sex:						
Female	17	68	20	80	0.94	0.33
Male	8	32	5	20		NS

SD: Stander deviation t: Independent t test χ^2: Chi square test NS: Non significant (P>0.05)

Table 2: Thyroid hormones level among the two studied groups

Variable	Cases (n=25)	Control (n=25)	Test	P
FT3:			**MW**	**
Mean ± SD	3.27 ± 1.2	4.59 ± 1.47	**3.11**	**0.002**
Median	3.5	4.2		
Range	0.93 – 5.5	2.9 – 10.1		
FT4:			**t**	**
Mean ± SD	14.5 ± 1.46	17.24 ± 4.49	**2.90**	**0.006**
Median	14.5	16.1		
Range	12.1 – 18.11	10.10 – 31.9		
TSH:			MW	
Mean ± SD	1.60 ± 1.17	2.15 ± 3.15	0.36	0.72
Median	1.5	1.6		NS
Range	0.11 – 3.6	0.1 – 16.44		

SD: Stander deviation MW: Mann Whitney test NS: Non significant (P>0.05) **: Highly significant (P<0.01) Ft3 :free triiodothyronine Ft4 : free thyroxine TSH: thyrotropin

Table 3: Correlation between Thyroid hormones parameters and age, EDSS, No of T2 lesions and relapse among cases group

Variable	Free T3 (n=25)		Free T4 (n=25)		TSH (n=25)	
	R	**P**	**r**	**P**	**R**	**P**
Age (years)	-0.39	0.05 NS	0.21	0.32 NS	-0.21	0.32 NS
Duration (years)	**-0.46**	**0.02***	0.32	0.12 NS	-0.12	0.56 NS
EDSS	**-0.62**	**0.001****	0.06	0.78 NS	-0.05	0.74 NS
No.of relapse	**-0.46**	**0.02***	0.10	0.62 NS	0.11	0.60 NS
No of T2 lesions	-0.35	0.09 NS	**-0.46**	**0.02***	-0.30	0.15 NS
FT3	---	----	0.32	0.12 NS	**-0.50**	**0.01***
FT4	0.32	0.12 NS	----	---	**-0.41**	**0.04***
TSH	**-0.50**	**0.01***	**-0.41**	**0.04***	----	----

r: Pearson's correlation coefficient NS: Non significant (P>0.05)
*: Significant (P<0.05) **: Highly Significant (P<0.01)
EDSS :Expanded Disability Status Scale

Table 4: Relation between Thyroid hormones and Disease modifying therapy (DMT) among cases group

Variable	ttt(DMT)	N	Mean	SD	Range		Test	P
FT3	**No**	14	2.90	1.25	0.93	5.50	**MW**	
	Yes	11	3.75	1.01	1.10	4.80	**2.08**	**0.04***
FT4	**No**	14	14.14	1.38	12.10	16.60	t	
	Yes	11	14.96	1.50	12.60	18.11	1.40	0.17 NS
TSH	**No**	14	1.18	1.01	0.11	3.42	MW	
	Yes	11	2.11	1.20	0.50	3.60	1.56	0.12 NS

SD: Stander deviation MW: Mann Whitney test t: Independent t test
NS: Non significant (P>0.05) *: Significant (P<0.05) DMT :Disease modifying therapy

Table 5: Relation between Thyroid hormones parameters and disease course and gadolenium enhancement in MRI among cases group

Variable	Course	Enhancement.	N	Mean	SD	Range		Test	P
FT3	**Relapse**	**Enhanced.**	15	3.10	1.26	1.10	5.50	MW 0.68	0.39 NS
	Remission	**Not**	10	3.52	1.13	0.93	4.80		
FT4	**Relapse**	**Enhanced.**	15	14.42	1.31	12.10	16.60	t 0.33	0.47 NS
	Remission	**Not**	10	14.62	1.73	12.50	18.11		
TSH	**Relapse**	**Enhanced.**	15	1.46	1.06	0.11	3.50	MW 0.56	0.58 NS
	Remission	**Not**	10	1.79	1.36	0.11	3.60		

SD: Stander deviation MW: Mann Whitney test t: Independent t test
NS: Non significant (P>0.05) Ft3 :free triiodothyronine Ft4 : free thyroxine TSH: thyrotropin

Table 6 : Relation between Thyroid hormones level and disease severity(EDSS) among cases group

Variable	EDSS	N	Mean	SD	Range		Test	P
FT3	**Mild**	11	3.82	0.72	1.5	5.50	**K**	
	Moderate	10	3.3	1.20	0.93	3.2	**8.65**	**0.01***
	Severe	4	1.68	1.04	0.93	5.5		
FT4	**Mild**	11	14.56	1.38	12.80	18.11	F	
	Moderate	10	13.85	1.61	12.10	16.6	0.47	0.63 NS
	Severe	4	14.5	1.5	12.50	15.2		
TSH	**Mild**	11	2.04	1.08	0.77	3.60	K	
	Moderate	10	1.29	1.27	0.11	3.50	3.38	0.19 NS
	Severe	4	1.13	0.96	0.12	2.07		

SD: Stander deviation K: Kruskal Wallis test F: ANOVA test
NS: Non significant (P>0.05) *: Significant (P<0.05) EDSS :Expanded Disability Status Scale
Mild :(0-3) Moderate: (3.5-5.5) Severe: (6-9.5)

DISCUSSION

Thyroid hormones are critical for CNS development, which is involved in progenitor cell proliferation and differentiation they are also essential for CNS myelination and may be important for remyelination [**20].**

Thus we designed this study to investigate the serum thyroid hormones (Ft3 ,Ft4, TSH) levels in 25 MS patients compared with 25 age and sex matched healthy controls and to assess relationship between them and characters of the disease , treatment status and clinical features of RRMS. We observed in this study that ages of patients ranged from 19 years to 50 years with mean age of (37.4 ± 8.03) which go in line with Acar et al **[1]** study. Several studies had reported gender differences in risk of developing MS [**21].** In our study, we found an increased percentage of females (68%) than males (32%) similar to Lunde et al **[22].**

In our present work we found that there were no statistical significance difference between the two

studied groups in Free T4 and TSH but there was statistical significance decrease in frequency of Free T3 level among cases group. Elżbieta and Andrzej **[23]** also reported low serum T3 level coexisting with normal T4 and TSH levels in both men and women with MS. They supposed that these concentrations may indicate changed peripheral conversion pathway of thyroid hormones in MS.

Regarding TSH, Aylin et al **[24],** reportd that TSH values were statistically lower among patients compared to those in healthy controls which is against our results. They also found no statistical significant difference between TSH levels and EDSS which is in line with our results.

Kiessling et al **[25]** in their case control study on thyroid function in MS has demonstrated significantly increased T4 levels and lower TSH levels which is against our results and agree with us in the low level of FT3 .They also reported that these changes in thyroid function parameters were similar in different MS courses and did not correlate with the degree of clinical disability.

In our study there was a negative significant correlation between Free T3 and duration, EDSS, and number of relapse. Also there were –ve significant correlation between Free T4 and number of T2 lesions. Niederwieser et al **[26]** reported that MS patients with hypothyroid diseases were significantly older but they did not differ significantly in disease duration and EDSS.

Jiang et al **[27]** is the only study to demonstrate a direct relationship between levels of iodothyronines and EDSS but in CSF. They used reverse T3 and indicated that an abnormal thyroid hormone may exist within the brain in MS patients. They reported that EDSS was significantly correlated with CSF rT3 (reverse T3) levels and (total) TT4/ rT3 ratio in MS patients. They studied rT3 which is an inactive metabolite, and do not activate the TH receptor, and has no influence on oligodendrocyte differentiation, which can contribute to improvement of disability of MS. Therefore they used CSF rT3 levels and CSF TT4/ rT3 molar ratios as useful markers of underlying disease activity.

In our study there was a decrease in Free T3 among cases without medical treatment compared to treated cases with DMT (IFN-β1a) but there was no statistical significance differences in between them in free T4 and TSH level. However, Durelli et al **[28]** reported in their study 156 multiple sclerosis patients that the frequency of thyroid dysfunction during interferon-beta treatment showed random, non-significant changes over time. Both incident thyroid autoimmunity and dysfunction frequently occur in MS patients during IFN-β (1a and 1b) therapy [**29].**

We also found no statistical significance differences between free T3, T4 or TSH level and disease course and gadolenium enhancement in MRI among cases group. Munteisa et al **[30]** also found no association between thyroid disorders and the clinical course of MS and EDSS throughout the follow-up period.

Results of our study showed statistical significance decrease in FT3 in severe cases compared to mild and moderate cases. But there were no statistical significance differences in between them in free T4 or TSH level. The studies which demonstrate a direct relationship between levels of iodothyronines and EDSS are rare **[27].** Niederwieser et al **[26]** reported that MS patients with hypothyroid diseases did not differ significantly in disease duration and EDSS.

CONCLUSION

Thyroid hormones are critical for CNS development, as they are involved in progenitor cell proliferation and differentiation. They are also essential for CNS myelination and may be important for remyelination.

Our study demonstrates a decrease in the level of thyroid hormone (Free T3) among cases and a negative significant correlation between Free T3 and EDSS. According to the role of Free T3 in remyelination and –ve correlation between it and EDSS it may be helpful if used in MS treatment.

Recommendations: Further Studies on large samples of multiple sclerosis, including different types of MS are needed to detect the role of T3 in the treatment of MS.

Conflict of Interest: None.

Financial Disclosures: None.

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