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Research Article

Assessment of Thyroid Functions in Multiple Sclerosis Patients Treated with Disease Modifying Therapies

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ABSTRACT

Background: Multiple sclerosis is a chronic disease believed to be the result of autoimmune disorders of the central nervous system, characterised by inflammation, demyelination, and axonal transection, affecting primarily young adults.
Objective: The study aim is to evaluate the impact of disease-modifying treatments on thyroid functions and thyroid autoantibodies with subsequent effects on the outcome of the disease.
Subjects and Methods: A retro prospective study enrolled 45 patients who were diagnosed in the Multiple Sclerosis Clinic according to the revised McDonald criteria (2017). Blood samples for thyroid functions and autoantibody tests were taken before, 3 months and after 6 months from the start of disease modifying therapy. The Expanded Disability Status Scale was used to assess the severity of the disease before and after 6 months of receiving treatment.
Results: Forty five patients with the mean age of 33.3 years, a standard deviation (SD) of ± 9.5 years were enrolled in this study. (64.4%) patients' age was between 20 - 39 years.
The mean free T3 decreased significantly, while the mean anti-TPO and anti-TG increased after three months compared to its baseline level.
After six months of treatment, the mean free T4 decreased significantly, while the mean TSH increased compared to its baseline level. There were no significant correlations between the baseline (EDSS) score and after 6 months of therapy.
Conclusion: Thyroid hormone dysfunction and thyroid autoimmune antibody levels that changed in response to interferon beta therapy in patients with multiple sclerosis may be temporary and not associated with poor outcomes.

Introduction

Multiple sclerosis is a chronic disease, believed to be the result of immune disorders of the central nervous system, characterized by inflammation, demyelination, and axonal transection, affecting primarily young adults causing a range of debilitating symptoms that can significantly impact a person's quality of life (1). Remitting relapse multiple sclerosis (MS) is the most common type of MS in general and affects 97% of people with the disease onset earlier than 18 years old (2). For many years, treatment options for MS were

limited, with no effective cure available. However, in recent years, disease-modifying therapies (DMTs) have been developed that can slow the progression of the disease, reduce relapse rates, and improve the overall health and well-being of people living with MS (3).

There are several types of DMTs available, each with its own unique mechanisms of action and potential benefits and risks. These include interferon beta, glatiramer acetate, dimethyl fumarate, teriflunomide, fingolimod, natalizumab, alemtuzumab, and ocrelizumab, while these drugs have shown promising results in clinical trials, they are not without side effects, and determining which DMT is the most appropriate for an individual patient can be a complex and challenging process (4).

Interferon beta is one of the most widely used therapies for MS because it has been shown to modulate the immune cells activity, including T and B cells, which are important for the defense of the body against infections. Furthermore, it has been shown to have anti-inflammatory properties, which may be beneficial for the treatment of autoimmune diseases such as MS (5).

Autoimmune thyroid diseases have been found to be more prevalent among MS patients and their first-degree relatives. (6) Despite some variability in the results of the studies, it is important to note that while several studies establishing that interferon beta would not cause the induction of thyroid autoantibodies in MS patients (7, 8), other studies highlight its effect in thyroid dysfunction (9, 10). By shedding light on this important topic, we hope to enhance the understanding of the complex interactions between MS, interferon beta therapy, and thyroid dysfunction - whether it affects multiple sclerosis outcome - and ultimately improve patient care.

Subjects and methods

This retro prospective cohort study was done at Azadi Teaching Hospital in Kirkuk Multiple Sclerosis Clinic starting from 1 October 2022 and ending on 1 May 2023.

Sixty-six patients were the total number of patients who were registered in the Multiple Sclerosis Clinic who were diagnosed with (MS) according to the revised McDonald criteria for 2017 (11), 10 patients refused to participate, 11 patients were excluded from the study because they had a history of chronic disease (stroke, thyroid disease, liver or kidney disease, dementia), recent surgery, or on chronic medications that can affect thyroid hormone levels before 3 months of study, while the remaining 45 patients were enrolled in this study.

The Expanded Disability Status Scale (EDSS) (12) was used to estimate the severity of the disease before and after 6 months of receiving treatment, the scale is used to quantify the disability of eight functions, pyramidal, cerebellar, cerebral, brain stem, visual, sensory, intestine and bladder functions, and other functions performed by the patients. Patients were classified by severity of disease into mild (0-3), moderate (3.5-5.5), and severe (6-9.5).

Blood samples withdrew for thyroid function (TFT), and thyroid autoantibody tests before, 3 months, and after 6 months from the start of disease-modifying therapy: Free triiodothyronine (FT3), free thyroxin (FT4), thyroid stimulating hormone (TSH), antithyroglobulin antibody (ATG), and thyroperoxidase antibody (TPO-Ab) were measured using (Cobas Roche 6000) kits and analysed by using a Cobas machine analyser with c501model - clinical chemistry analyser and the e601 model immunoassay analyser with normal value for (FT3) is 3.1-6.8 pmol / l 'Kit Ref. no. 09007725190", (FT4) is 12-22 pmol / l 'Kit Ref. no. 09007741190", and (TSH) is 0.270-4.20 uIU / mL 'Kit Ref. no. 08429324190", (ATG) is <115 IU/ml "Kit Ref. no. 57476402", (TPO-Ab) is <34 IU/ml "Kit Ref. no. 60701302".

Statistical analysis done by using the Statistical package for social sciences (SPSS) version 26. The data are presented in the form of average, standard deviation, and range. Categorical data presented by frequency and percentage. Paired t tests are used to compare thyroid autoantibodies and thyroid hormones (TFTs) before and after treatment. The Pearson correlation test (r) was used to evaluate the correlation between the EDSS, thyroid hormones and thyroid autoantibodies. The level of a P value below 0.05 is considered to be significant.

According to the 2013 WMA Helsinki Declaration, all ethical issues were approved. Approval was obtained from the Clinical Research Ethics Committee of the University of Kirkuk - College of Medicine -Kirkuk- Iraq (decision no. 19, date 15-11-2022). An informed written agreement was taken from all participants prior to enrolment in the study, as well as an ethical agreement from the hospital administrator.

Results

Forty five were enrolled in the study. The age of the studied patients ranged from 14-52 years with a mean of 33.3 years and a standard deviation of ± 9.5 years. (64.4%) patients' age was between 20 - 39 years. The proportion of females was higher than that of males (75.6% versus 24.4%) with a female to male ratio of 3.09:1. (Table 1).

Table 1: Distribution of the studied cases according to the demographic characteristics

Variable	No. (n= 45)	Percentage (%)
Age (year)		
< 20	4	8.9
20 – 39	29	64.4
≥ 40	12	26.7
Mean ± SD	33.3 ± 9.5	
Sex		
Males	11	24.4
Females	34	75.6

The distribution of study patients according to (EDSS) and (DMT) that was used shows in (Table 2), the (EDSS) score before treatment was between (1.0 – 4.5) in 71.1% of patients and (1.0 – 4.5) in 75.6% after 6 months of treatment.

Betaferon (interferon beta 1b) was used in 60% of the patients compared to 40% of Avonex (interferon beta 1a) as a disease-modifying therapy.

Table 2: Distribution of studied patients according to the expanded disability status scale and disease modifying therapy

Variable	No. (n= 45)	Percentage (%)
EDSS before treatment		
1.0 – 4.5	32	71.1
5.0 – 9.5	13	28.9
Mean ± SD	3.46 ± 1.4	
EDSS after six months' treatment		
1.0 – 4.5	34	75.6
5.0 – 9.5	11	24.4
Mean ± SD	3.33 ± 1.4	
Disease modifying agent		
Betaferon (interferon beta 1b)	27	60.0
Avonex (interferon beta 1a)	18	40.0

The comparison in (TFT) and thyroid autoantibody levels before and after treatment is shown (Tables 3 and 4). The mean (FT3) decreased significantly (3.61 versus 3.86 pmol/l, P= 0.009); while the means (anti-TPO) and (anti-TG) increased after 3 months compared to baseline (35.22 vs 20.72 IU / ml, P = 0.001; and 108.04 vs 78.35 IU/mL, P =0.001 respectively).

After 6 months of therapy, the mean (FT4) decreased significantly (16.14 versus 15.21 pmol/l, P= 0.004); while the mean (TSH) increased compared to before treatment (3.09 vs 2.84 mlU/ml, P= 0.001).

Table 3: Comparison in thyroid functions and thyroid autoantibodies before and after three months' treatment

Variables	Time		P-value †
	Baseline Mean ± SD	3 months after treatment Mean ± SD	
FT3 (pmol / l)	3.86 ± 0.5	3.61 ± 0.4	0.009*
FT4 (pmol / l)	16.14 ± 2.0	15.89 ± 2.2	0.519
TSH (mlU/ml)	2.84 ± 0.6	2.86 ± 1.2	0.903
Anti-TPO (IU / ml)	20.72 ± 18.1	35.22 ± 27.6	0.001*
Anti-TG (IU/ml)	78.35 ± 28.3	108.04 ± 40.3	0.001*

† Paired t-test, * Significant (p<0.05), FT3=free triiodothyronine, FT4=free thyroxin, TSH=thyroid stimulating hormone, ATG=antithyroglobulin antibody, TPO-Ab=thyroperoxidase antibody

Table 4: Comparison in thyroid functions and thyroid autoantibodies before and after six months' treatment

TFTs	Time		P-value †
	Baseline Mean ± SD	6 months after Rx Mean ± SD	
FT3 (pmol / l)	3.86 ± 0.5	3.88 ± 0.4	0.842
FT4 (pmol / l)	16.14 ± 2.0	15.21 ± 1.5	0.004*
TSH (mlU/ml)	2.84 ± 0.6	3.09 ± 0.5	0.001*
Anti-TPO (IU / ml)	20.72 ± 18.1	21.7 ± 14.8	0.322
Anti-TG (IU/ml)	78.35 ± 28.3	78.72 ± 26.4	0.75

† Paired t-test, * Significant (p<0.05), FT3= free triiodothyronine, FT4=free thyroxin, TSH=thyroid stimulating hormone, ATG=antithyroglobulin antibody, TPO-Ab=thyroperoxidase antibody.

Three was no significant statistical correlations (P ≥ 0.05) between the baseline EDSS score, (TFT) and thyroid autoantibodies (Table 5).

Table 5: The Correlation between the baseline EDSS score with thyroid function and autoantibodies.

Variables	Baseline EDSS score	
	r	P – value †
FT3 (pmol / l)	-0.074	0.631
FT4 (pmol / l)	-0.008	0.957
TSH (mlU/ml)	-0.132	0.398
Anti-TPO (IU / ml)	-0.103	0.499
Anti-TG (IU/ml)	-0.071	0.641

†Pearson correlation coefficient, EDSS = Expanded Disability Status Scale, FT3= free triiodothyronine, FT4=free thyroxin, TSH=thyroid stimulating hormone, ATG=antithyroglobulin antibody, TPO-Ab=thyroperoxidase antibody.

Discussion

Multiple sclerosis is one of the common cause of nervous system disabilities in young adults and has a global prevalence of about 2.8 million, which has increased significantly over the past decade (13). (MS) is an immune mediated disorder that affects selectively the myelin of the central nervous system, leading to nerve fibers damage; this is probably related to the genetic architecture (14).

The present study shows that most patients with multiple sclerosis were between 20-39 years of age. This age group is considered the peak age of MS onset, which is similar to the other studies (15, 16).

The study shows that the proportion of females higher than that of males (75.6% versus 24.4%) with a ratio of female to male of 3:1, that is typical of what is mentioned in several studies (17, 18, 19) , the reason for the higher incidence and prevalence of MS in women compared to men is not fully understood, but its thought to be multifactorial, probably related to hormonal, genetic, and environmental factors (15).

Management of MS aims to reduce the risk of recurrence and possible progression of disability, but to date there is no curative treatment (20). The available disease-modifying therapies (DMTs) are generally can be classified as medium-efficacy (ME) DMT (dimethylfumarate, interferon beta, glatiramer acetate, teriflunomide) and high efficacy (HE) DMT (fingolimod, cladribine, alemtuzumab, siponimod, ocrelizumab, natalizumab, and newly approved ofatumumab and ozanimod) (21).

Interferon beta is the first line (DMT) that it's recommended for remitting relapse multiple sclerosis type in more than 90 countries because its economically more convenient than other lines, and easily implemented by most insurance systems in those countries (22).

There is no clear consensus on whether MS treatment treatment butffects thyroid function and autoantibody levels, according to our results, it is worthy to note that the level of (FT4) significantly decreased while (TSH) increased in our patients after six months of receiving the treatment compared to baseline levels although it's still in the normal range, which was similar to A systematic review and meta-analysis of endocrine abnormalities associated with interferon therapy which found that the proportion of hypothyroidism was higher than that of hyperthyroidism (23, 24), on the other hand, the anti-TPO and anti-TG have increased significantly in our patients

after three months of receiving the treatment, but return to near its previous level after 6 months of therapy, which is consistent with the other studies that performed by (Monzani et al., 1999) (25) and (Caraccio et al., 2005) (26). This can be explained by the fact that interferon beta maintains the anti-inflammatory status of the immune system. Because it modulates the immune regulatory system, it can cause autoimmune disorders. As a result, interferon beta therapy is associated with a high risk of thyroid disease, and or autoimmunity (27), another explanation is that (IFN-β) can stimulate chemokine ligand 10 secretion by human thyrocyte cells, a prototype of Th-1 chemokine, which has been shown to play a pathogenic role in MS and autoimmune thyroiditis (28).

This study didn't find any significant correlation between the baseline (EDSS) with thyroid hormone dysfunction and autoimmune antibodies (Pearson correlation coefficient P value > 0.05), in addition to that, changes in baseline (EDSS) compared to 6 months after treatment with interferon beta were not significant.

The limitation of this study is that only two types of DMT were used in the Kirkuk MS clinic and the relatively short follow-up period, which may be a point at which further future research is needed to show the net effect of all types of DMT on thyroid profiles in longer time frames and in different types of MS.

Conclusion

Thyroid hormone dysfunction and thyroid autoimmune antibody levels that changed in response to interferon beta therapy in patients with multiple sclerosis may be temporary and not associated with poor outcomes.

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This research did not receive any specific fund.

Conflict of Interest

Authors declare no conflict of interest

Data availability

Data are available upon reasonable request

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