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Original Article

Thyroid autoimmunity in patients with multiple sclerosis before and after treatment

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Abstract

Introduction: Thyroid dysfunction is observed in a number of patients with multiple sclerosis (MS) before or after starting treatment. Considering the high prevalence of autoimmune thyroid diseases in general population, the cause-and-effect relationship of MS or the treatments in patients with thyroid problems is doubtful. Present research was designed to clarify the issue in a geographical location that has not been investigated so far and to find whether the occurrence of thyroid disease is an early phenomenon or not?

Methods: Descriptive-analytical study was performed on 324 patients with MS in Tabriz, Iran. The participants were selected based on the inclusion/exclusion criteria through convenience sampling from patients referred to the neurology clinics of Tabriz university of medical sciences. Thyroid function tests were performed for the patients to diagnose thyroid problems. In these patients, the relationship between laboratory test results and the medications used for the treatment and control of MS was obtained using inferential statistical tests. P-value <0.05 was considered statistically significant.

Results: FT3 and FT4 levels consistently increased, except for interferon beta 1b. Changes in thyroid-stimulating hormone (TSH) levels were reduced for fingolimod and interferon beta 1a, while they increased for other treatments. The decrease in levels of anti-thyroglobulin and anti-thyroid peroxidase after treatments was found to be non-significant.

Conclusion: Significant changes in thyroid function may occur following pharmacotherapy of MS, at least for fingolimod and interferon beta 1a. It is recommended to periodically perform thyroid function tests before and after starting treatment.

Introduction

Multiple sclerosis (MS) is the most common chronic inflammatory autoimmune disease of the central nervous system,[1,2] including the brain and spinal cord, characterized by chronic demyelination and axonal loss in these tissues.[3] Some researchers believe that MS results from the interaction between genetic factors, immune system regulators, and infectious agents.[4] However, conclusive evidence for this hypothesis is still lacking.[5] The concomitant presence of autoantibodies and other autoimmune disorders supports the role of autoimmune processes in MS physiopathology.[6,7] Damage to myelin in the central nervous system interferes with the transmission of neuronal messages between the brain, spinal cord, and other parts of the body, leading to the manifestation of the primary symptoms of MS depending on the injury site.[8,9] The recovery and recurrence patterns of MS are as relapsing-remitting, progressive-relapsing, primary-progressive, and secondary-progressive.[10-12]

The association of MS with systemic and localized autoimmune diseases has been repeatedly reported. Specific autoantibodies have been identified in MS patients.[13] Autoimmune thyroid disease is one of the most common disorders studied in these patients, and recently, the reports of higher anti-thyroid autoantibodies, which were unrelated to treatment, has been on the rise in patients with MS.[14] The importance of thyroid diseases falls within the fact that they may impair the myelination process, accelerating the progression of MS and causing disability in these patients.[15,16] Therefore, in recent years, thyroid disorders and anti-thyroid antibodies have been extensively studied.[17] The results of some studies support the role of thyroid autoimmunity, and others suggest the role of immunosuppressive drugs, including interferons, in the development of thyroid dysfunction in MS.[18] However, various investigations reported a prevalence of thyroid hormonal disorders as 2.5%-10% and the prevalence of thyroid autoantibodies as 4%-21%.[19,20]

Some recent studies have noted a relatively high prevalence of hypothyroidism in patients with MS, suggesting a link between hypothyroidism and MS, which needs more research to be confirmed.[21,22] Considering

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contradictory results about the possible link between thyroid autoimmunity and MS, lack of similar studies in Iran, and the rising trend of MS in our region and country, we aimed to determine the true incidence of thyroid functional disorders and autoimmunity in patients with MS. We address the question of whether thyroid disease is a primary or secondary (i.e., related to medications) phenomenon in these patients. The status of patients was screened and compared pre- and post-treatment, and according to the results, a number of solutions were proposed for the current challenges in managing MS.

Methods

Study design

This descriptive-analytical study was conducted in 2017 on the population of patients with MS registered in the MS Association of Tabriz. Participants were selected by the convenience sampling method after being appraised for the inclusion/exclusion criteria.

Inclusion/exclusion criteria

The inclusion criteria were having an active profile in the center (regular visits and receiving medications), a definitive diagnosis of MS, and giving consent to participate in the study; It's important to note that the patients signed the written informed consent form before participating in the study. The exclusion criteria encompassed receiving corticosteroids, the change of treatment regimen during the study, as well as a history of thyroid diseases, surgery, and receiving radioactive iodine for hypothyroidism.

Sample size

A total of 324 patients with MS, including 83 males and 241 females, were initially evaluated in this study. Among 83 male patients who participated in this study, 52 (62.65%), 8 (9.63%), 3 (3.61%), 6 (7.22%), 5 (18.05%), and 9 (10.84%) were treated with interferon beta-1a, interferon beta-1b, fingolimod, glatiramer acetate, rituximab, and dimethyl fumarate, respectively. A definite MS diagnosis was not established in one male patient, excluded from the study. In addition, 13 patients were excluded due to a history of receiving corticosteroids. Four of the patients were excluded owing to being under treatment for thyroid problems, and 27 were excluded because of not cooperating. Due to changing the treatment regimen and receiving corticosteroids, 13 other individuals were eliminated. Finally, 25 men with MS were evaluated.

Among 241 female patients who participated in this study, 178 (73.85%), 12 (4.97%), 28 (11.61%), 7 (2.9%), 4 (1.65%), and 12 (4.97%) received interferon beta-1a, interferon beta-1b, fingolimod, glatiramer acetate, rituximab, and dimethyl fumarate, respectively. Out of the women enrolled initially, the reasons for exclusion were a history of receiving corticosteroids (n = 34), thyroid problems (n = 17), and refusing to participate (n = 90). Out of 100 female patients finally enrolled, 32 and 26 individuals were excluded from the study due to the lack of timely referral for clinical examinations and the changing of the therapeutic regimen, respectively. Therefore, 42 women with MS were analyzed at the end of the study, and the final analysis was performed on 25 men and 42 women (a total of 67 patients).

Study protocol

All the patients referred to the specialized MS clinic and the MS Association of Tabriz during 2017, and were definitively diagnosed with MS based on the McDonald diagnostic criteria, were included in this study. All the patients were tested for functional thyroid disorders by thyroid-stimulating hormone (TSH) and free thyroxine (FT4), and thyroid autoimmunity based on anti-thyroid peroxidase (TPO) and anti-thyroglobulin (TG) tests at admission. In the case of no contraindications, the patients underwent routine treatments for neurological diseases and were followed up by reassessing thyroid function and autoimmunity 3 and 6 months after starting the treatment.

Thyroid dysfunction was categorized as the subclinical and clinical forms of hypothyroidism or hyperthyroidism. Clinical hypothyroidism was defined as TSH ≥ 10 μg/mL, and subclinical hypothyroidism as the TSH level of 4.5-10 μg/mL. Clinical hyperthyroidism was diagnosed when TSH fell below the normal range, and subclinical hyperthyroidism was defined as a lower-than-normal TSH level along with normal FT4. Patients with clinical hypothyroidism or hyperthyroidism underwent treatment. Thyroid autoimmunity was diagnosed with a one-time positive result for thyroid autoantibodies, but the diagnosis was ruled out if autoantibody levels were below the normal laboratory references.

Serum TSH, FT4, and free triiodothyronine (FT3) concentrations were measured by chemiluminescent immunoassay, and normal ranges were considered 0-5.5 mu/L, 2-8.8 ng/dL, and 230-619 pg/dL, respectively. Anti-thyroid antibodies, namely anti-TPO and anti-TG, were also assessed by chemiluminescent immunoassay.

Ethical considerations

This study was approved by the Ethics Committee of Tabriz University of Medical Sciences. After acquiring ethical approval, the researcher referred to Imam Reza Educational and Medical Center of Tabriz. After talking to the head of the Neurology, Rheumatology, and Endocrinology ward, the researcher collaborated with the MS Association of East Azerbaijan Province to recruit patients. The objectives of the study were explained to all participants, and they were requested to sign an informed consent form. No costs were charged for the laboratory tests.

Data analysis

All the data extracted from patients' files were entered into the SPSS software version 21. Clinical presentations

were compared between different MS treatment groups using the t-test. The incidence of thyroid disorders was described by means and percentages, and the pre- and post-treatment rates were compared applying the chi-square test. *P* value < 0.05 was considered statistically significant. It is worth noting that in this study, the "*P* values" are compared between the beginning and the end of the study, indicating an assessment of changes over time.

Results

The mean ± standard deviation of age in men was 31.49 ± 5.89 years. 17 people (68%) of them took interferon beta 1a, 3 people (12%) interferon 1b, 2 people (8%) were fingolimod, 2 people (8%) rituximab and 1 person (4%) recieved dimethyl fumarate. The mean age of the female participants was 34.89 ± 8.59 years, and 26 (63.41%), 5 (12.19%), 5 (12.19%), 3 (7.31%), and 2 (4.84%) of these women were under treatment with interferon beta-1a, interferon beta-1b, fingolimod, rituximab, and dimethyl fumarate, respectively. Comparing the mean age between men and women showed no statistically significant difference ($P = 0.548$). According to the Chi-square test, there was no statistically significant difference between men and women regarding the types of medications received ($P = 0.241$). Regarding the possible confounding effects of medications on the levels of thyroid hormones, the changes of thyroid hormones were separately evaluated for each medicine.

Evaluation of changes in the hormones FT3, FT4, TSH, Anti TG, and Anti TPO before receiving interferon beta-1a showed that only one case of clinical hypothyroidism with TSH:13.3, which was both anti-TPO positive (51.7) and Anty TG positive (643) was observed; There was also a case of subclinical hypothyroidism with TSH: 4.9 among patients. FT3 and FT4 levels were in the normal range (from the beginning of the study to six months after receiving the drug), while FT3 levels increased significantly over time with a non-significant increase of 5%. There was a significant increase in the FT4 levels of 2.3% ($P = 0.045$) over the last 6 months. Also, except for one case at all times, TSH levels were below 4.5 for all participants; The lowest was seen in six months after treatment. Changes in TSH during interferon beta-1a were associated with a non-significant decrease of 11%. In the study of autoantibodies among interferon beta 1a recipients, there were two cases of anti-TG positive and one case of anti-TPO positive, which were also positive in the first and second trimesters after follow-up; Anti-TPO levels increased significantly over time, increasing by 1.3%, while anti-TG levels decreased in the first trimester after receiving interferon beta 1a, but in the interval. The third month to the sixth month has increased, which was equal to 0.8% (Table 1).

Evaluation of changes in FT3, FT4, TSH, Anti TG and Anti TPO before receiving interferon beta-1b showed that suffering from all functional and autoimmune tests was one of two subclinical hypothyroid cases with TSH of 4.7 and 4.8. Were within the normal range; However, FT3 and FT4 levels have been significantly reduced over time, with a 1.2% decrease in FT3 levels and a 0.9% decrease in FT4 levels, respectively, and TSH levels after receiving the drug during the second and third quarters were accompanied by a non-significant increase; It should be noted that the increase in TSH was estimated at 1.3%. The range of autoantibody levels at baseline was normal in all interferon-1b recipients; Only one case of anti-TPO positive was seen in the first and second trimesters after treatment, which coincided with an increase in TSH (TSH:4.6); In the other patients, the levels of antibodies were associated with a non-significant increase, so that the increase was in anti-TPO with 0.7% and in anti-TG with 0.8 percent, respectively (Table 2)

Examination of changes in the hormones FT3, FT4, and TSH before receiving fingolimod showed that the range of all thyroid function tests was within the normal range; Examination of thyroid autoimmune tests (anti-TPO and anti-TG) before receiving fingolimod showed that there was a positive anti-TPO case among patients. During the treatment period, TSH levels at all times were below 4.5 for all participants treated with fingolimod, and the

Table 1. Comparison of changes in the hormones studied at different time intervals in patients treated with interferon beta-1a

Variable		Before treatment	Three months post-treatment	Six months post-treatment	*P* value
FT_3	Mean	251.25 ± 11.1	266.28 ± 11.01	275.3 ± 55.96	0.098
	Min-Max	173-189	199-288	205-300	
FT_4	Mean	38.12 ± 1	65.25 ± 1	24.33 ± 2	0.045
	Min-Max	1-1.55	1.01-1.22	1.49-2.67	
TSH	Mean	88.25 ± 3	62.2 ± 3	22.12 ± 3	0.145
	Min-Max	2.58-4.45	2.24-4.11	1.85-3.98	
Anti-TG	Mean	56.66 ± 8.1	85.35 ± 7.1	12.12 ± 9.12	0.558
	Min-Max	6.5-11.45	5.47-9.87	7.65-11.45	
Anti-TPO	Mean	47.33 ± 7	33.41 ± 8	69.01 ± 10.1	0.077
	Min-Max	5.29-9.55	6.78-10-95	8.95-15.45	

FT_3: Free triiodothyronine; FT_4: Free thyroxine; TSH: Thyroid-stimulating hormone; Anti-TG: Thyroglobulin antibodies; Anti-TPO: Anti-thyroid peroxidase; Min: Minimum; Max: Maximum.

lowest was seen in six months after treatment; It should be noted that changes in TSH levels similar to autoantibodies were associated with a non-significant decrease and the rate of decrease was 0.8%. It was also observed that FT3 and FT4 levels increased significantly over time with $P=0.045$ and $P=0.041$, respectively; It should be noted that the rate of increase for each was equal to 1.1% and 0.55%, respectively. It should be noted that the levels of antibodies during fingolimod treatment were associated with a non-significant decrease and the rate of changes in anti-TPO by 0.8% and anti-TG by 0.51% was significant (Table 3).

Examination of changes in the hormones FT3, FT4, TSH, anti-TG, and anti-TPO before receiving rituximab indicated that the range of all tests was normal; Over time, the levels of functional tests (FT3, FT4 and TSH) have been significantly increased with an increase of 0.75%, 0.50% and 1.1%, respectively. It should be noted that TSH levels at all times for all participants receiving rituximab were below 4.5, the lowest level was seen six months after treatment. The levels of autoantibodies (anti-TPO and anti-TG) have been associated with a non-significant decrease over time, with a reduction of 0.8% for anti-TPO and 1.1% for anti-TG, respectively (Table 4).

Examination of changes in FT3, FT4, TSH, anti-TG, and anti-TPO before receiving dimethyl fumarate indicated that the range of all tests was within the normal range. It was also observed that FT3, FT4 and TSH levels increased insignificantly over time; So that the increase of FT3, FT4 and TSH was equal to 2.3%, 1.5% and 0.9%, respectively. It should be noted that TSH levels at all times for all participants treated with this drug were below 4.5, the lowest level was seen before the start of treatment, while changes in autoantibody tests over time after receiving this drug It was accompanied by a non-significant decrease so that their levels were reduced by 1.2% (Table 5).

There was no significant relationship between age group and thyroid disorders in patients with MS treated with various medications ($P=0.817$). In other words, age was not a key determinant in developing thyroid disorders in patients with MS. However, in terms of gender, it was found that the incidence of thyroid disorders was significantly higher in women than in men receiving MS medications ($P=0.044$).

Discussion

The results of the present study showed that only the intake of interferon beta-1a and fingolimod can lead to

Table 2. Comparison of changes in the hormones studied at different time intervals in patients treated with interferon beta-1b

Variable		Before treatment	Three months post-treatment	Six months post-treatment	*P* value
FT_3	Mean	314.31±21.14	307.28±45.65	298.25±12.01	0.145
	Min-Max	273-355	247-341	225-315	
FT_4	Mean	45.02±1	87.33±1	55.24±1	0.245
	Min-Max	1.85-2.47	1.15-2.44	1.13-2.29	
TSH	Mean	66.41±2	55.01±3	14.65±3	0.259
	Min-Max	2.05-3.39	2.36-4.08	1.99-4.01	
Anti-TG	Mean	25.55±9.1	96.61±10.1	31.75±12.1	0.099
	Min-Max	7.39-12.25	8.55-14.43	8.47-16.75	
Anti-TPO	Mean	66.41±9	48.69±10	52.01±14.1	0.052
	Min-Max	7.77-11.37	7.59-12-30	12.24-18.65	

FT_3: Free triiodothyronine; FT_4: Free thyroxine; TSH: Thyroid-stimulating hormone; Anti-TG: Thyroglobulin antibodies; Anti-TPO: Anti-thyroid peroxidase; Min: Minimum; Max: Maximum.

Table 3. Comparison of changes in the hormones studied at different time intervals in patients treated with fingolimod

Variable		Before treatment	Three months post-treatment	Six months post-treatment	*P* value
FT_3	Mean	314.21±31.41	269.31±24.96	321.35±42.1	0.045
	Min-Max	254-342	189-236	287-403	
FT_4	Mean	0.01±0.45	1.59±0.63	2.34±0.89	0.041
	Min-Max	1.22-2.59	1.11-2.89	1.86-3.44	
TSH	Mean	3.89±0.55	3.56±0.37	3.21±0.30	0.415
	Min-Max	2.58-4.43	2.75-4.35	2.51-4.22	
Anti-TG	Mean	7.22±1.41	6.14±1.02	5.48±0.88	0.125
	Min-Max	5.69-9.63	4.85-9.03	3.95-7.15	
Anti-TPO	Mean	5.01±0.48	4.85±0.33	4.12±0.19	0.293
	Min-Max	4.14-9.00	3.96-6-30	3.45-5.69	

FT_3: Free triiodothyronine; FT_4: Free thyroxine; TSH: Thyroid-stimulating hormone; Anti-TG: Thyroglobulin antibodies; Anti-TPO: Anti-thyroid peroxidase; Min: Minimum; Max: Maximum.

Table 4. Comparison of changes in the hormones studied at different time intervals in patients treated with rituximab

Variable		Before treatment	Three months post-treatment	Six months post-treatment	*P* value
FT_3	Mean	308.18 ± 48.95	315.19 ± 15.62	320.19 ± 68.03	0.233
	Min-Max	265-356	271-369	248-375	
FT_4	Mean	1.81 ± 0.41	1.99 ± 0.71	2.01 ± 0.85	0.659
	Min-Max	1.33-2.62	1.41-2.96	1.75-3.37	
TSH	Mean	3.22 ± 0.41	3.54 ± 0.33	3.25 ± 0.63	0.396
	Min-Max	2.74-4.29	2.87-4.13	2.73-4.03	
Anti-TG	Mean	7.01 ± 1.39	6.85 ± 1.14	6.50 ± 0.99	0.514
	Min-Max	5.77-8.18	4.96-9.15	4.77-8.15	
Anti-TPO	Mean	5.00 ± 0.51	4.84 ± 0.41	4.41 ± 0.29	0.293
	Min-Max	4.25-8.32	3.36-6-66	3.59-6.19	

FT_3: Free triiodothyronine; FT_4: Free thyroxine; TSH: Thyroid-stimulating hormone; Anti-TG: Thyroglobulin antibodies; Anti-TPO: Anti-thyroid peroxidase; Min: Minimum; Max: Maximum.

Table 5. Comparison of changes in the hormones studied at different time intervals in patients treated with dimethyl fumarate

Variable		Before treatment	Three months post-treatment	Six months post-treatment	*P* value
FT_3	Mean	289.96 ± 20.78	299.85 ± 21.41	311.52 ± 22.63	0.415
	Min-Max	231-326	245-364	291-411	
FT_4	Mean	1.81 ± 0.55	1.95 ± 0.78	2.02 ± 0.96	0.896
	Min-Max	1.15-2.49	1.63-2.85	1.63-3.03	
TSH	Mean	3.15 ± 0.26	3.48 ± 0.30	3.59 ± 0.066	0.409
	Min-Max	2.81-4.17	2.91-4.43	3.03-4.14	
Anti-TG	Mean	6.98 ± 1.39	6.90 ± 1.10	6.75 ± 1.02	0.696
	Min-Max	5.77-8.18	4.96-9.15	4.77-8.15	
Anti-TPO	Mean	5.01 ± 0.63	4.92 ± 0.55	4.66 ± 0.41	0.559
	Min-Max	4.15-7.12	4.14-6-96	3.95-6.03	

FT_3: Free triiodothyronine; FT_4: Free thyroxine; TSH: Thyroid-stimulating hormone; Anti-TG: Thyroglobulin antibodies; Anti-TPO: Anti-thyroid peroxidase; Min: Minimum; Max: Maximum.

significant changes in thyroid hormones, while other drugs used do not have a significant effect on thyroid hormones. Of course, it should be noted that changes in free T3 and free T4 levels, except for interferon beta-1b, have always been increasing. Changes in TSH levels for fingolimod and interferon beta 1a have been decreasing, while levels for other drugs have been increasing, along with changes in autoantibody levels. There has been an increase in interferons and a decrease in other drugs.

In a study by Ruck et al, it was noted that the levels of thyroid hormones altered in newly diagnosed MS cases after at least three months of consuming interferon beta-1a.[23] Rotondi et al showed that receiving interferon beta-1b increased T3 and T4 hormones significantly, which was attributed to the mechanism of action of this drug and was in agreement with our results.[24] The consumption of interferon beta leads to the production of antibodies against the medicine. Therefore, these antibodies can affect the immune system and may be involved in developing autoimmunity coupled with the elevation of T3 and T4 hormones. However, the exact mechanism of this phenomenon is yet to be disclosed in further studies.

Ruck et al found that the incidence of thyroid disorders in patients with MS was remarkably higher in those treated with beta-interferons than in patients taking other drugs.[8] The changes ensuing from the use of interferon beta, such as antibody production, modify cellular signaling, compromises drug effectiveness and sensitizing the immune system. These alterations may activate the endocrine system to boost the function of the immune system, leading to a rise in thyroid hormones.

According to the results of Muller et al the incidence of thyroid disorders was about 81% lower in patients receiving interferon beta-1a than in patients taking interferon beta-1b, which was attributed to the lower absorption of this medication and was in line with our observation.[25] Gonzalez-Aguilera et al reported that beta interferons (both 1a and 1b) could accelerate the rise of thyroid hormones at a faster pace than other drugs used to treat MS, which may result in the development of thyroid disorders in long-term owing to the induction of antibodies. The mentioned results were in line with the findings of the current investigation.[26]

In a study conducted by Muller et al the prevalence of hypothyroidism was reported to be higher in patients with MS (7%) than in healthy individuals (2%), necessitating the regular screening of these patients for thyroid disorders. Resolving hypothyroidism may also result in

better therapeutic outcomes in MS. The results of the latter study were consistent with our findings.[9] Many studies of the role of MS medications in the development of thyroid disorders revealed that none of the medications used to treat MS were associated with thyroid disorders in patients without a personal or family history of thyroid problems.[27-29] These results contrasted our observation that indicated significant changes in thyroid hormones after receiving interferon beta-1b (30).

The limitations of our study included a small sample size and the lack of long-term follow-up. It is recommended to address these limitations in future studies. Furthermore, regarding the negative impacts of interferon beta-1b on thyroid hormones, it is suggested to periodically check thyroid hormones in the patients treated with this medicine.

Conclusion

According to the results of the present study, none of the medications routinely used to treat MS could significantly change thyroid hormones except for interferon beta-1a and fingolimod.

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Author's Contribution

Conceptualization: Marhamat Mohammad Jafari, Hormoz Ayromlou, Halimeh Amirazad, Akbar Aliasgharzadeh.

Writing–review & editing: Marhamat Mohammad Jafari, Hormoz Ayromlou, Halimeh Amirazad, Akbar Aliasgharzadeh.

Competing Interests

The authors do not have any conflict of interest to declare.

Ethical Approval

This study was approved by the Ethics Committee of Tabriz University of Medical Sciences. After acquiring ethical approval (No: IR.TBZMED.REC.1398.499).

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Study Highlights

What is current knowledge?

Thyroid autoimmune diseases have different responses in pre- and post-treatment and following the use of different drugs.

What is new here?

According to the results of the present study, none of the medications routinely used to treat MS could significantly change thyroid hormones except for interferon beta-1a and fingolimod.

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