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ORIGINAL ARTICLE

The Overexpressed NF-κB p65 mRNA Mediated Coexistence of Multiple Sclerosis and Hashimoto' Thyroiditis

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ABSTRACT

Background: Multiple sclerosis (MS) has been considered a T cell–mediated autoimmune demyelinating disorder. Nuclear factor κB (NF-κB) is one of the master transcription factors that regulate the activity of inflammatory cells the present study aimed to investigate the NFKB/P65 mRNA levels in patients with MS and to assess its role in the prediction of Hashimoto' thyroiditis (HT).

Methods: 50 patients with clinically definite relapsing-remitting multiple sclerosis (according to the McDonald criteria 2017) compared to 50 healthy age and sex-matched controls. Thyroid serum antibodies, IgG index (IgG), and oligoclonal band (OCB) were assessed. The relative expression of NFKB/P65 mRNA was measured using real-time quantitative PCR.

Results: there were significantly higher values of NFKB/P65 mRNA levels in patients with HT (2.4±0.54) compared to other patients without HT (1.3±1.45) and control group (0.8±0.17), p <0 .001**.** Significant associations were confirmed between NFKB/P65 mRNA correlated to thyroid autoimmunity and MS manifestations, p <0. 001 .Linear regression revealed that only FT4 and TSH were independent variables correlated with NFKB/P65 mRNA, p < 0.001. Regarding prediction of MS, ROC curve revealed that the sensitivity of NFKB/P65 mRNA was 96 %, and specificity was 88% at cutoff 0.98 with (95% CI = 0.909–0.999).Concerning HT prediction, the cutoff 1.42 with (95% CI = 0.843–1.000)with a sensitivity of 93.8 % and, a specificity of 87.4%.

Conclusions: NFKB/P65 mRNA increased in patients with MS more specifically in HT. Thus, NFKB/P65 mRNA could be used as noninvasive prediction markers of MS and HT.

Keywords: Hashimoto' Thyroiditis; Multiple Sclerosis; oligoclonal band; Nuclear factor κB; thyroid peroxidase.

INTRODUCTION

It has been demonstrated that Multiple sclerosis (MS) is a demyelinating autoimmune disease, with an unclear etiological mechanism. An intriguing observation is that MS is characterized by lymphocyte infiltration, several inflammatory patterns, and axonal loss [1]. The demyelination process in MS is characterized by oligodendrocytes damage, and autoimmune alteration [2]. Indeed, it has been reported that MS is characterized by variation in the levels of proinflammatory cytokines, for example, TNF-α, and the anti-

inflammatory cytokines in particular IL-6, and these variations are responsible for remission and recovery periods [3]. Hashimoto's thyroiditis (HT), which is chronic lymphocytic thyroiditis [4]. The most common manifestations of HT comprise extensive lymphocyte infiltration, follicular collapse, and follicular cell degeneration [5]. Many studies have revealed that HT is characterized by enlargement of the thyroid gland with serum antithyroglobulin antibody (TGAb) and thyroid peroxidase antibody (TPOAb) [6]. It has recently been shown that irregular treatment of patients will lead to structural damage which leads to a sequence of diseases, such as hyperthyroidism, hypothyroidism, thyroid nodules, and thyroid cancer [7]. It is worth mentioning that transcription factor NF-κB is controlling the expression of several genes implicated in cell survival, cell death, inflammation, proliferation, and cell differentiation [8]. Additionally, the role of Activation of NF-κB has been found in MS brain tissue, where it is restricted to brain cells and infiltrating macrophages in or near CNS lesions [9]. It should be emphasized that NF- κB has an essential role in both innate and adaptive immune responses. An intriguing observation detected that NF-κB is one of the main transcription factors that is activated by many receptors for example cytokines receptors; consequently, numerous studies have established its involvement in the development of autoimmune diseases [10]. Despite these pieces of evidence, there is a substantial gap in our knowledge about the role of NFKB/P65 mRNA in prediction of MS and HT . Therefore, the current working hypothesis aims to investigate the NFKB/P65 mRNA levels in patients with MS and to assess its role in the prediction of HT.

PATIENTS AND METHODS

This case-control study enrolled 100 participants, fifty age- and sex-matched healthy controls, and fifty drug-naïve patients with relapsing-remitting MS (RRMS) fulfilling the diagnostic criteria for MS according to the revised McDonald's criteria 2010 [11].This study was conducted in the Outpatient Clinics of Neurology Department and Diabetes and Endocrinology unite of Internal Medicine Department , Zagazig University Hospital . All patients were subjected to full medical history taking, thorough clinical neurological examination, and assessment of disease severity by the Expanded Disability Status Scale (EDSS) at the initial assessment visit [12]. Routine diagnostic analyses were carried out according to Zagazig University Hospital. Written informed consent was obtained from all participants and the study was approved by the research ethical committee of the Faculty of Medicine, Zagazig University. (Ethics number. 10898), The work has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for students involving humans.

We investigated both albumin and IgG in serum and CSF ,then an albumin quotient and IgG quotient and IgG index (IgG quotient / albumin quotient) were determined. oligoclonal band (OCB) were assessed using isoelectric focusing (IEF) on agarose gel, followed by immunoblotting. Real-time quantitative PCR for NF-κB p65 mRNA expression PCR primers was designed using Oligo 6.0 software and synthesized by Shanghai Sangon. NF-κB p65 primers: forward: 5′-ATCCCATCTTTGACAATCGTGC-3′, reverse: 5′-CTGGTCCCGTGAAATACACCTC-3′, and amplification product is 153 bp. GAPDH primers: forward: 5′-GCACCGTCAAGGCTGAGAAC-3′, reverse: 5′-TGGTGAAGACGCCAGTGGA-3′, and amplification product is 138 bp. Peripheral blood mononuclear cells were isolated using density gradient centrifugation and total RNA was extracted using TRIzol reagent (Invitrogen, USA). The relative amounts of NF-κB and GAPDH mRNA were expressed as $2^{-\triangle CT}$ ($\triangle$CT=CT value of the target gene - CT value of internal control).

Statistical analysis

Data are presented as the mean ± standard deviation. Statistical comparisons among multiple groups were performed using a one-way analysis of variance (ANOVA) followed by a post hoc Test for further evaluations. $p < 0.05$ were considered statistically significant. All statistical analyses were performed using SPSS software (version 22.0; IBM Corp.). The normality of variables was confirmed with the Kolmogorov-Smirnov test. For the variables that are not normally distributed, the Mann-Whitney U test was used. The associations of NFKB/P65 mRNA levels with other parameters were tested with the Spearman and Pearson correlation, and further evaluation of independent factors correlated with NFKB/P65 mRNA levels in the MS group was investigated with a linear regression test. The diagnostic power of NFKB/P65 mRNA levels was explored by the ROC test.

RESULTS

In the present research, 50 patients with MS who their diagnosis were according to Mc Donald criteria 2017.MS group including 30 patients without HT and 20 patients with HT in addition to 50 control subjects, age and sex were matched and all participants were evaluated clinically, laboratory, and radiologically as shown in table 1. The clinical and laboratory characteristics of the studied patients are summarized in Table 1.

Table 1 Clinical and laboratory characteristics of studied groups

Characteristics	Control group(n=50)	MS without thyroiditis (n=30)	MS with thyroiditis, (n=20)	P
Age (years)	31.4±6.4	29.7±6.3	33.3±5.4	**0.167**
Sex (Male/female)	15/35	10/20	6/14	**0.197**
Disease duration/year	-	5.4±1. 7	7.5±1.4	**<0.001***
Number of relapses in the last 2 years	-	5.1±1.97£	6.5±3.97$	**<0.001***
Clinical picture of MS				
Sensory	-	17(56.7%)	13(65%)	**0.556**
Motor	-	8(26.7%)	5(25%)	**0.895**
Cerebellar	-	7(23.3%)	4(20%)	**0.780**
Speech	-	5(16.7%)	2(10%)	**0.659**
Visual	-	14(46.7%)	5(25%)	**0.127**
EDSS	-	1.6±1.2	4.01±0.97	**<0.001***
SBP (mmHg)	118.9±8.9	118.6±11.6	119.2±5.4	**0.972**
DBP (mmHg)	77.08±8.3	76.1±9.5	77.3±5.3	**0.837**
ESR (mm/h)	13.5±5.3	63.5±9.3£	83.5±11.78$, &	**<0.001***
WBC count (cell × 10^3µl)	5.59±0.5	5.6±0.53	6.9±1.2$, &	**<0.001***
FT3(pg/ml)	1.87±0.12	0.75±0.13£	0.56±0.08$, &	**<0.001***
FT4(ng/dl)	1.6±0.17	0.54±0.11£	0.34±0.09$, &	**<0.001***
TSH (µIU/ml)	3.5±0.3	4.1±0.95£	5.5±1.3$, &	**<0.001***
Anti TPO(IU/ml)	26.3±8.3	207.5 ±33.4£	389.1 ±82.2$, &	**<0.001***
Anti TG(IU/ml)	39.6±22.3	395.4±88.6£	476.4±94.5$, &	**<0.001***
IgG index	-	0.69±0.55£	1.51±6$	**<0.001***
OCB (count)	-	6.1±3.88£	14.5±5.97 &	**<0.001***
NFKB/P65 relative expression level	0.8±0.17	1.3±1.45£	2.4±0.54$, &	**<0.001***

MS; Multiple sclerosis, EDSS; Expanded Disability Status Scale, SBP; systolic blood pressure; DBP; diastolic blood pressure, , FPG; fasting plasma glucose .OCB ;oligoclonal band, IgG index; immunoglobulin G index n, Nuclear factor κB (NF-κB). , * P < 0.001 when compared MS patients with control group.

£ Significant P values (P < 0.05) when comparing the control group with patients without HT.

$ Significant P values (P < 0.05) when comparing the control group with patients with HT.

&Statistically significant P values (P < 0.05) when comparing patients without HT with patients with HT.

There were significantly higher values of thyroid autoimmunity and MS manifestations in patients with HT (n=30) compared to other studied groups, p <0. 001. Whereas, There were significantly lower values of FT3 and FT4, in patients with HT compared to other studied groups < .001. **As shown in Figure 2**, our study revealed that there were significant higher values of NFKB/P65 mRNA levels in patients with HT (2.4±0.54) compared to other patients without HT (1.3±1.45) and control group (0.8±0.17), F= 129.144, p <0 .001.

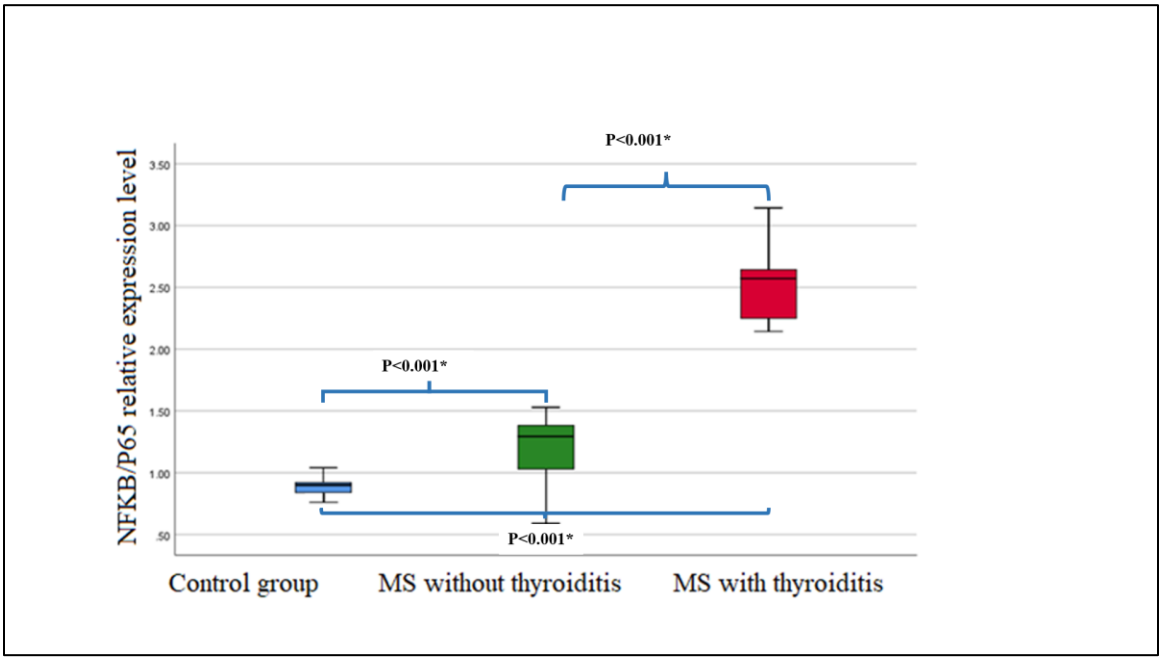

Figure 2: comparison between the relative expression of NFKB/P65 mRNA levels between studied groups.

To determine the correlations NFKB/P65 mRNA levels are shown **in Table 2.** We applied Pearson and Spearman correlation coefficient test to investigate the associations of parametric and non-parametric variables with NFKB/P65 mRNA levels and we detected that there were positive correlations with disease duration/year, number of relapses in the last 2 years, sensory manifestations, and visual manifestations of MS, EDSS, ESR, TSH, anti-TPO and anti-TG, $p < .001$. Although, we found negative correlations between NFKB/P65 mRNA and FT3 as well as FT4,$p < 0.001$.

Table 2: Pearson correlation coefficient between circulatory NFKB/P65 mRNA relative expression levels with other studied parameters of among MS patients.

Characteristics	NFKB/P65 mRNA	
	r	p
Disease duration/year	0.458	<0.001*
Number of relapses in the last 2 years	0.676	<0.001*
Clinical picture of MS		
Sensory	0.458	<0.001*
Motor	0.030	0.835
Cerebellar	0.061	0.672
Speech	0.050	0.729
Visual	0.443	<0.001*
EDSS	0.727	<0.001*
WBC	0.212	0.139
ESR	0.347	<0.001*
FT3	-0.420	<0.001*
FT4	-0.395	<0.001*
TSH	0.454	<0.001*
Anti TPO	0.561	<0.001*
Anti TG	0.543	<0.001*

*P < 0.05

Meanwhile, to further examine the independent associations of NFKB/P65 mRNA levels as shown **in Table 3**. We used a linear regression test and we found that only FT4 and TSH were independently correlated with NFKB/P65 mRNA, p <0 .001. Eventually, we verified whether NFKB/P65 mRNA could be used as non-invasive diagnostic markers for the prediction of MS, particularly in patients with HT.

Table 3: linear regression analyses to test the influence of the main independent variables against circulatory NFKB/P65 levels (dependent variable) in MS patients.

Model	Unstandardized Coefficients		Standardized Coefficients	t	P value	95% C.I.	
	B	S.E	Beta			Lower Bound	Upper Bound
(Constant)	1.113	0.573		1.942	0.059	-0.042	2.269
FT4	0.730	0.731	0.130	0.998	0.324	-0.744	2.203
TSH	-0.428	0.179	-0.771	-2.393	<0.05*	-0.788	-0.067
Anti TPO	0.006	0.003	0.996	2.422	<0.05*	0.001	0.012
EDSS	0.115	0.063	0.394	1.835	0.073	-0.011	0.242
Disease duration/year	0.013	0.041	0.039	0.320	0.750	-0.070	0.097

*P < 0.05

As shown in Figure 3a and 3b, respectively. We performed an ROC curve analysis test to differentiate between the control and MS group, and we investigated the diagnostic power of NFKB/P65 mRNA in comparison to known diagnostic markers of MS which are IgG index and OCB and we demonstrated that the AUC of NFKB/P65 mRNA, IgG index and OCB was 0.954 (95% CI = 0.909–0.999), 0.669, (95% CI = 0.547–0.791) and 0.980, (95% CI = 0.941–1.000), respectively. Furthermore, the cutoff values of NFKB/P65 mRNA were 0.98 with sensitivity = 96 %, and specificity = 88%. The cutoff values of the IgG index were 0.129 with sensitivity = 82 %, and specificity = 66%. Intriguingly, the cutoff values of OCB were 0.7 with sensitivity = 97 %, specificity = 100%, p < .001 **Figure 3a.**

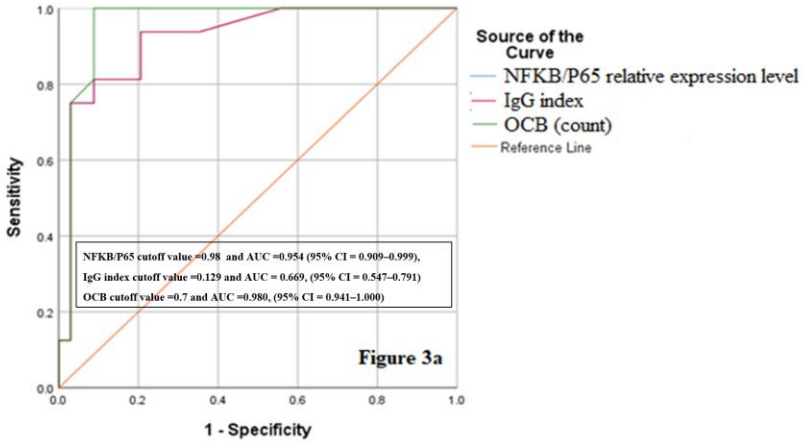

Figure 3 a: ROC curve of NFKB/P65 mRNA, IgG index and OCB levels for prediction of patients with MS among studied groups.

Concerning differentiation between MS patients with and without HT, the AUC of NFKB/P65 mRNA IgG index and OCB was 0.922 (95% CI = 0.843–1.000),0.920, (95% CI = 0.840–1.000) and

0.961, (95% CI = 0.907–1.000), respectively. Furthermore, the cutoff values of NFKB/P65 mRNA were 1.42 with a sensitivity of 93.8 % and, a specificity of 87.4%. The cutoff values of the IgG index were 0.564 with a sensitivity of 80 % and, a specificity of 97.4%. Interestingly, the cutoff values of OCB were 0.72 with a sensitivity of 95.8 % and, a specificity of 92%, p < .001 **Figure 3b.**

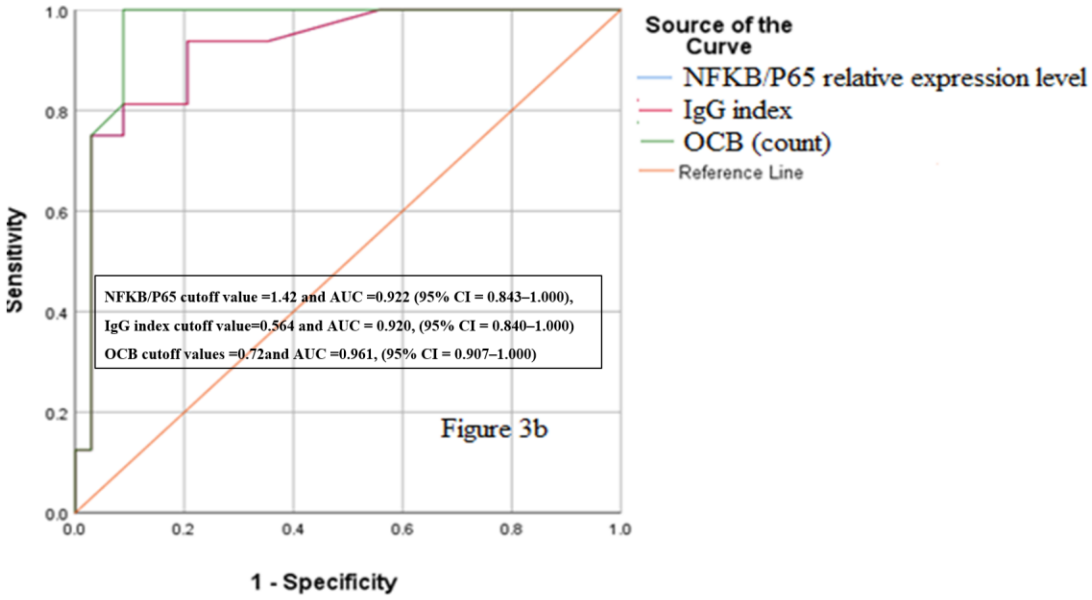

Figure 3 b: ROC curve of NFKB/P65 mRNA, IgG index and OCB levels for differentiation of patients with HT among MS patients.

DISCUSSION

Our previous data showed that there is crosstalk between MS and HT [13]. As it is generally believed that both MS and HT is an autoimmune disease with T-cell-mediated inflammation associated with various clinical and pathological features [14]. It has been shown that MS patients treated with interferon-β may develop laboratory signs of autoimmune thyroid disease [15]. Likewise, thyroid hormones have an important role in CNS myelination and re-myelination [16]. A consistent and accurate diagnosis of MS is perilous for allowing early interventions and preventing disease progression [17]. Based on these findings, we conducted this research to discover noninvasive prognosis predictive markers of MS and HT. Here, we shed light on the role of NFKB/P65 mRNA in the prediction of MS. In recent years, profuse studies provided strong evidence that dysregulated gene expression plays an important role in autoimmune diseases such as MS and HT [18]. In this study, age and sex were matched between the groups because these variables could affect the gene expression levels. According to the results shown in Table 1, disease duration/year, number of relapses in the last 2 years, EDSS, ESR, WBC, thyroid function, and thyroid autoimmune tests were significant differences between the studied groups (p < 0.001). While the clinical picture of MS was a non-significant difference between the studied groups (p>0.05). Accumulating evidence demonstrates that NF-κB can alter the expression of other genes and can contribute to different autoimmune diseases [19], as seen in the pathogenesis of Graves' orbitopathy [20]. Therefore, this study aimed to explore the NFKB/P65 mRNA levels in patients with MS and to measure its role in the prediction of HT. To the best of our knowledge, this study is the first Egyptian study conducted to examine the NFKB/P65 mRNA levels in patients with MS and particularly patients with HT. Curious results demonstrated that there were significantly higher values of NFKB/P65 mRNA levels in patients with HT compared to other patients without HT and the control group < 0.001. In agreement with the above data, Yan et al confirmed that patients with progressive MS had high levels of

circulatory NF-κB similar to RRMS in comparison to the control group [21]. Similar results were observed by Chen and his colleagues, they observed overexpression of NF-κB in MS and they added that after treatment of MS with immune-modulating drugs the levels of NF-κB were decreased [22]. Thus, they suggested that NF-Kb could be used as a diagnostic and prognostic marker of MS. Our studies also revealed that there were positive associations between NFKB/P65 mRNA and disease duration/year, number of relapses in the last 2 years, sensory manifestations, and visual manifestations of MS, EDSS, ESR, TSH, anti-TPO and anti-TG, p <0. 001. Even though, we observed negative correlations between NFKB/P65 mRNA, FT3, and FT p <0 .001. On the contrary, Fitzner et al found no association between NFKB/P65 and severity of MS as assessed by EDSS [23]. The discrepancy between the two studies' results could contribute to different designs and sample sizes. Meanwhile, to further examine the independent associations between studied variables and NFKB/P65 mRNA we applied a linear regression test, and we detected that only FT4 and TSH were independent variables correlated with NFKB/P65 mRNA, p < 0. 001. An interesting study conducted by Liu et al confirmed high levels of NFKB/P65 mRNA in HT by in vitro and in vivo study. Moreover, they detected that Dihydroartemisinic could be used for the treatment of thyroiditis by inhibiting the NF-kB signaling pathway [24].

It has been shown that OCB [25] and IgG index [26] are the most commonly used today in the diagnosis of MS but till now they are still invasive and not completely detected in MS [27]. An intriguing discovery was that NFKB/P65 mRNA levels could be used as non-invasive diagnostic markers for the prediction of MS, particularly in patients with HT. We provide evidence suggesting that the diagnostic power of NFKB/P65 mRNA in the prediction of MS in comparison to the IgG index and OCB was significantly high. Also, these results confirmed that NFKB/P65 mRNA had a sensitivity of 96 % and specificity of 88%. Whereas the IgG index sensitivity was 82 % and specificity was 66%. Additionally, we further confirmed that the OCB sensitivity was 97 % and the specificity was 100%, p <0. 001. It was interesting regarding the discrepancy between MS patients with and without HT. We speculated that the NFKB/P65 mRNA sensitivity was 93.8 % and specificity was 87.4%. Although IgG index sensitivity was 80 % and specificity was 97.4%. Mysteriously, the OCB sensitivity was 95.8 % and the specificity was 92%, p <0 .001. Overall, our findings suggest that the diagnostic power of NFKB/P65 mRNA in the diagnosis of MS was very high similar to other invasive markers" CSF OCB and IgG index.

CONCLUSION

Thus, In conclusion, our current study highlighted the important roles of NFKB/P65 mRNA in the prediction of patients with MS and HT and revealed that NFKB/P65 mRNA increased in patients with MS and HT. Interestingly, their levels were significantly correlated to thyroid dysfunction and MS manifestations. And so, they could be used as noninvasive markers of MS and HT.

Study Strengths and Limitations

This study has several unique strengths. To date, according to our information, no study examined the role of NFKB/P65 mRNA in the diagnosis of MS and HT among Egyptian patients. Our study also has a few potential limitations. Small sample size and the study enrolled Egyptians only, therefore, it remains unclear whether our findings apply to other ethnic groups. Thus, we recommend further research on a large sample size of participants from different ethnicities.

Authors' contributions

NMR, MHAG, DRI, and MOW gathered participants' characteristics. MAA investigated the participants. All the authors have significant contributions to the conception of the work; revising it critically for intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work.

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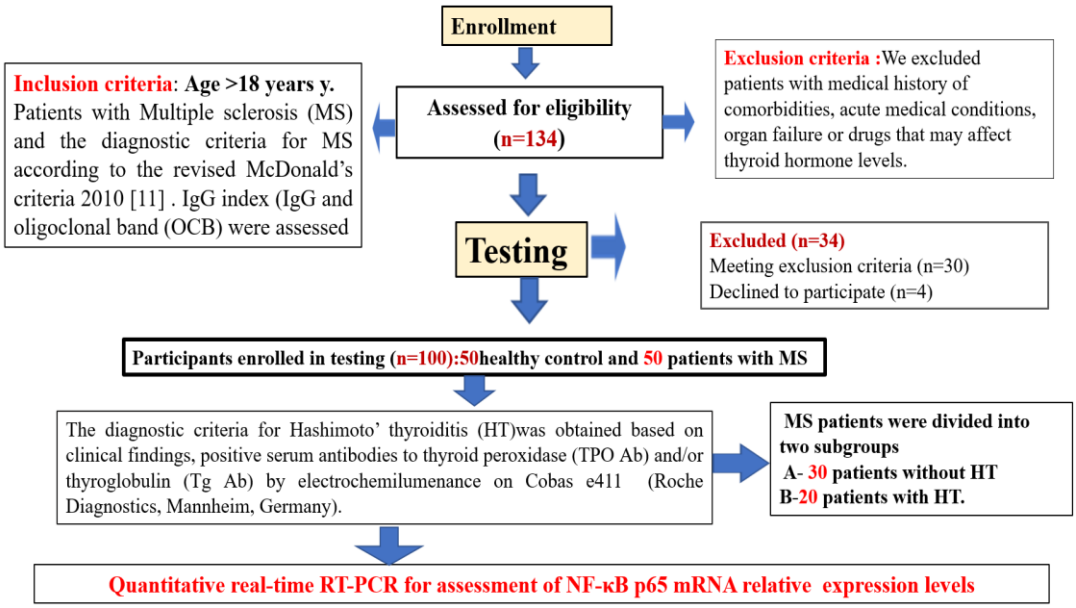

Figure (S1): flowchart of the study

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