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Research Article

Correlation of Epstein Barr virus Infection and Related Immune Response among Iraqi Patients with Hashimoto's Thyroiditis

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I N F O

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A B S T R A C T

Background: Hashimoto's thyroiditis (HT) is an autoimmune thyroid disorder and the leading cause of hypothyroidism in developed countries. It commonly affects women (10:1 ratio) between the ages of 30 and 50, with a prevalence of about 2% and an annual incidence of 0.3-1.5 cases per 1,000 people. HT's etiology is multifactorial, involving genetic and environmental factors. Recent research suggests viral infections, particularly Epstein-Barr virus (EBV), may trigger HT. EBV, a DNA virus targeting B lymphocytes, can modulate the immune system and is linked to HT development.

Objective: To explore the affiliation of HT with EBV infection and related immune response

Method: serum samples from 60 newly diagnosed as HT patients (51 females and 9 males) and 60 healthy controls, (48 females and 12 males), were obtained and tested by the indirect Chemiluminescence Immunoassay (CLIA) for both anti-EBV-VCA IgG and anti-EBV-VCA IgM and by Enzyme-linked Immunosorbent Assay (ELISA) for both IFN-γ and IL-17.

Results: The results showed that there was no significant difference in anti-EBV-VCA IgG levels, with a highly significant difference in anti-EBV-VCA IgM levels between the group of patients and healthy people. The results also showed an increase in the levels of both IFN-γ and IL-17 in the patient group compared to the healthy group.

Conclusion: Elevated levels of anti-VCA-IgM for EBV, IFN-γ and IL-17 in the patients with HT compared to the healthy controls suggest that active EBV infection and related immune response may have a role in the HT onset or progression.

Keywords: Hashimoto's Thyroiditis (HT), Epstein-Barr Virus (EBV), Interferon-Gamma (IFN-γ), Interleukin-17 (IL-17), Electrochemiluminescence Immunoassay (ECLIA), Enzyme-Linked Immunosorbent Assay (ELISA)

Introduction

Hashimoto's thyroiditis (HT) is a predominant autoimmune endocrine disorder responsible for the vast majority of hypothyroidism cases in developed countries with adequate iodine levels.[1] HT prevalence ranges from 0.3 to 1.5 cases per 1000 individuals, with a male-to-female ratio of 7 to 10.[2] The HT is characterised by the production of IgG-class autoantibodies that target thyroid glycoproteins thyroglobulin (Tg-Ab) and /or enzymes thyroid peroxidase (TPO-Ab), which are found in the thyroid.[1] The diagnosis of Hashimoto's thyroiditis (HT) can be confirmed when there is thyroid dysfunction and the presence of serum TPO-Ab or Tg-Ab.[3] Lymphocytic infiltration is a pathological alteration that can occur in the thyroid gland in individuals with HT. Unidentified stimuli stimulate CD4+ T cell, which targets the thyroid antigen. Upon activation of CD4+ cells, an immunological response is triggered, leading to the migration of T and B lymphocytes to the thyroid gland. This results in the production of plasma cells and the death of thyroid cells.[4] Multiple studies indicate that viral infection may serve as a potential trigger for HT.[5] Epstein-Barr virus (EBV) has been associated with HT.[6] The EBV, also known as HHV-4, is a widely prevalent virus that contains double-stranded DNA (dsDNA). It belongs to the gamma-1 herpes family, demonstrates a distinctive human tropism, and has the ability to cause cancer and modulate the immune system. Generating latent infection in B cells for life, remaining inactive in most individuals with sporadic reactivation, and expressing over 80 genes, EBV infection is highly prevalent in humans, with about 90% of individuals being carriers of the virus.[7] A theory suggests that in individuals who are genetically vulnerable, B-cells that are infected with the Epstein-Barr virus (EBV) infiltrate the thyroid gland. These B-cells then create autoantibodies and convey signals to autoreactive T-cells, which further contribute to the autoimmune response.[6] Typically, the EBV infection is regulated, particularly by cytotoxic CD8+ T-cells that eradicate actively dividing and lytically infected B-cells. Reduced EBV-specific CD8+ T-cell count can lead to impaired regulation of EBV. Autoimmune disorders are typically associated with an elevated CD4/CD8 ratio.[6] Interferon-gamma (IFN-γ) is essential for progressing Hashimoto's thyroiditis (HT). Thyroid infiltrating lymphocytes have increased levels of IFN-γ, which stimulates the programmed cell death of follicular cells.[7,8] IFN-γ is thought to have a vital function in the immune response to EBV, as it is noticeably increased in patients with Infectious Mononucleosis (IM).[9] Scientists have verified the connection between thyroid fibrosis and heightened levels of inflammatory mediators. An association was discovered between the existence of IL-17 and stromal fibrosis in the thyroid glands of individuals with HT, as reported by Li et al.[10] The study conducted by Altamemi et al showed a significant contribution of IL17 in both the development and severity of HT.[11] Research findings indicate that EBV DNA amplifies the production of IL-17 in autoimmune disorders when detected by endosomal Toll-like receptors.[12]

The current study aims to estimate the levels of Anti-EBV-VCA IgG and Anti-EBV-VCA IgM and two proinflammatory cytokines, IFN-γ and IL-17, in the serum of patients newly diagnosed by the specialist physician as HT patients and compare them with healthy individuals to further understand disease mechanisms and assess the role of those cytokines in the disease onset and progression.

Materials and Methods

Subjects

We conducted the current case-control study on the Iraqi population in the Thi-Qar Provinces. A total of 120 blood samples were collected in the period from August 2023 to February 2024 at Al-Nasiriyah Teaching Hospital and Souq Al-Shuyoukh General Hospital in Thi-Qar Provinces. The 120 individuals in this study were divided into two groups: the Patients Group, which consisted of 60 patients, 51 females and 9 males, with an age range of 11–67 years, newly diagnosed with HT by the specialist physician, and the Control Group, which included 60 healthy individuals, 48 females and 12 males, with an age range of 12 - 63 years, without symptoms or chronic disease. The control group volunteers were medical staff, blood donors, and visitors to the premarital screening unit.

Inclusion Criteria

All patients who were newly diagnosed by the specialist physician as suffering from HT were included in the current study. The specialist physician used the American Thyroid Association's (ATA) diagnostic criteria for diagnosing patients with HT.

Exclusion Criteria

The exclusion criteria consisted of:- patients who were previously diagnosed as suffering from HT and were under treatment, non-autoimmune hypothyroidism, patients with other autoimmune diseases, a history of thyroidectomy, nonthyroidal systemic disorders such as acute or chronic hepatic, renal, cardiovascular, and cerebrovascular disorders, and benign and malignant patients.

Sample Collection

A five millilitre venous blood sample was drawn from both studied groups of individuals. Blood was placed in a gel activator tube, left to clot in a 37 °C water bath, centrifuged for ten minutes at 3000 rpm, and separated into four equal aliquots. All samples were identified by ID numbers and stored at -20 °C until use.

Estimation of the Levels of Studied Markers

The indirect CLIA technique was used to quantitatively estimate the levels of Anti-EBV-VCA IgM and Anti-EBV-

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VCA IgG using a fully automated instrument, the Maglumi 800. The instrument and the kits were provided by Snibe Co., Ltd., China. As for IFN-γ and IL-17 levels, they were estimated by a sandwich enzyme-linked immunosorbent assay (ELISA) technique. The kits were provided by Sunlong, China. All manufacturers' instructions were followed during the current study.

Ethical approval

The medical ethics committees of Jabir Ibn Hayyan University for Medical and Pharmaceutical Sciences, Medical College, approved this study protocol. The Iraqi Ministry of Health, Thi-Qar Health Directorate, approved the study under the document number [153/2023, 24/7/2023]. The authors informed all participants about the study's objectives, and they verbally agreed to participate in the study.

Statistical analysis

The data for the current study was statistically analysed using SPSS 29 and Microsoft Excel 2021. The chi-square test was employed to compare the categorical variables at a p- value < 0.05, while the independent- samples t- test was used to compare the means of the numerical variables at a p- value < 0.05 as well.

Results

The results showed that the mean ± Standard Deviation (SD) of the age was 37.0 ± 12.9 years in the patients group. While the mean ± SD of age was 37.5 ± 12.9 years in controls. There were no significant differences in the mean ages of the patients and controls (p- value = 0.566).

In terms of the sex-based distribution of the research groups, the study group consisted of 51 females and 9 males, whereas the control group had 48 females and 12 males. Based on sex, the patient and control groups did not differ significantly (p- value = 0.352), whereas a significant difference was noticed in patent (p- value < 0.001) (Table 1).

The mean levels of anti-EBV-VCA antibodies in the patient group in comparison to the healthy group are displayed in Table 2.

The mean levels of IFN-γ and IL-17 in the patients compared to the healthy controls are displayed in Table 3.

The sex-based Distribution of anti-EBV-VCA Antibodies in the patient group is displayed in Table 4.

The sex-based Distribution of IFN-γ and IL-17 in the patient group is displayed in Table 5.

Table 1.Distribution of Participants According to Sex

Sex	Patients		Controls		Total	
	n	%	n	%	N	%
Male	9	15.0	12	20.0	21	17.5
Female	51	85.0	48	80.0	99	82.5
Total	60	50.0	60	50.0	120	100

Patients vs controls: $CalX^2$= 0.86 $TabX^2$= 3.84 df = 1 p value < 0.352
For patients only: $CalX^2$= 49.0 $TabX^2$= 3.84 df = 1 p value <0.001

Table 2.Levels of Anti-EBV-VCA Antibodies in the Study Groups

Parameter	Patients (n = 60)	Controls (n = 60)	p Value
	Mean ± S. D		
VCA-IgG (AU/ml)	42.25 ± 12.8	41.69 ± 9.71	0.791
VCA-IgM (AU/ml)	3.142 ± 1.07	0.247 ± 0.13	< 0.001

Table 3. Levels of IFN-γ and IL-17 in the Study Groups

Parameter	Patients (n = 60)	Controls (n = 60)	p Value
	Mean ± S D		
IFN-γ (pg/mL)	58.27 ± 10.4	32.70 ± 9.74	< 0.001
IL-17 (pg/mL)	143.5 ± 17.0	82.49 ± 8.45	< 0.001

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Table 4.Sex-Based Distribution of Anti-EBV-VCA Antibodies Levels in Patients

Parameter	Females (n = 51)	Males (n = 9)	p- value
	Mean ± S D		
VCA-IgG (AU/ml)	42.06 ± 13.7	43.33 ± 5.72	0.787$^{Non-Sig}$
VCA-IgM (AU/ml)	3.072 ± 1.02	3.538 ± 1.29	0.233$^{Non-Sig}$

Table 5.Sex-Based Distribution of IFN-γ and IL-17 Levels in Patients

Parameter	Females (n = 51)	Males (n = 9)	p- value
	Mean ± S D		
IFN-γ (pg/mL)	58.23 ± 10.3	58.4 ± 11.6	0.947$^{Non-Sig}$
IL-17 (pg/mL)	141.9 ± 16.3	152.1 ± 19.5	0.099$^{Non-Sig}$

Discussion

The EBV that has been reactivated possesses the capacity to stimulate the generation of thyroid antibodies and has been associated with a multitude of autoimmune symptoms.[6] Previous research has suggested that the fact that EBV infections are more common in people with HT could mean that EBV is a possible cause of HT.[13] The present investigation demonstrated a higher level of anti-EBV-VCA IgM antibodies in the HT group compared to the healthy group. An Egyptian study showed elevated anti-EBV-VCA IgM positive proportions in HT patients, which is consistent with our outcomes.[14] Additionally; our findings did not indicate a substantial difference in levels of anti-EBV-VCA IgG antibodies in the HT group compared to the healthy group. This observation contradicts the findings of Vrbikova et al.[15], who observed that individuals diagnosed with HT exhibited notably elevated levels of anti-EBV-VCA IgG compared to the controls. Furthermore, these findings are in contrast to the observations made by Thomas et al.[16], who found that children diagnosed with autoimmune thyroid disease exhibited a significant elevation of anti-EBV-EBV IgG compared to the controls (p value= 0.008). Barzilai et al. conducted a study that linked EBV to autoimmune diseases, supporting the notion that EBV is a well-known environmental component in the context of autoimmune disorders. [17] EBV invades B cells and has the potential to permanently infect a small proportion of them in individuals who are otherwise in good health.[15] We can employ two overarching pathways to elucidate the potential correlation between EBV infection and thyroid autoimmunity onset. There is empirical evidence suggesting that the virus has the potential to generate a deceptive antigenic stimulus, hence inducing the activation of autoreactive T cells. The second criterion is valid if there is evidence that the immune response to viruses gives the innate immune system a non-specific stimulus, which makes it easier for autoreactive T cells to become activated and multiply. The persistent innate immune response to viral infection can also contribute to autoimmunity.[18]

Janyga et al. found that IFN-γ is the mediator most strongly linked to AITD, particularly HT, even though it is not dependent on either Th1 or Th2 cells.[19] In addition, Cheng et al. observed that individuals with HT exhibited elevated levels of IFN-γ in comparison to the control group.[20] The findings of the present study were consistent with previous research,[21-24] which also documented elevated levels of IFN-γ in patients with HT in comparison to the control group. IFN-γ is a type of Th1 cytokine that is synthesised by CD4+ Th1 cells, CD8+ T cells, and NK cells. When IFN-γ is produced independently or in conjunction with other inflammatory cytokines, it stimulates the production of major histocompatibility complex (MHC) classes I and II on antigen-presenting cells (APCs) and other cells. Additionally, it enhances the expression of adhesion molecules, as well as specific chemokines and chemokine receptors, in order to attract T cells to the site of inflammation.[25] IFN-γ is a contributing factor in autoimmune thyroid disorders. The thyroid produces IFN-α, and increased levels of IFN-γ from infiltrating lymphocytes in the thyroid have been demonstrated to promote the death of thyroid follicular cells by activating caspases.[26,27] When the immunological response to Tg begins, T cells that are specific to the thyroid migrate to the thyroid and stimulate the production of IFN-γ, which leads to the development of MHC class-II molecules in the Thyrocytes.[28] This phenomenon leads to the proliferation of autoreactive T cells, resulting in an inflammatory response that leads to the buildup of activated CD4+ and CD8+ T cells, B cells, plasma cells, and macrophages in the thyroid gland, thereby initiating autoimmune reactions and thyrocyte distraction.[26,28] The results align with the Iranian study, indicating that individuals with HT had elevated levels of serum IL-17A compared to the control group.[29] In a study conducted by Cautha et al., it was found that children diagnosed with HT had elevated levels of IL-17A, suggesting the crucial role of IL-17A in the development of this condition.[30] A study conducted by Figueroa-Vega et al. revealed interesting findings regarding individuals diagnosed with HT.[31] The

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research showed that these individuals had elevated levels of IL-17+ lymphocytes, as well as increased IL-17 mRNA levels, in their blood and thyroid tissue compared to the control group. In addition, the findings align with the viewpoints of other researchers.[32-34] Another study found that patients with HT showed higher mRNA levels of IL-17 and INF-γ in both peripheral blood mononuclear cells and thyroid tissue when compared to controls.[35] The presence of increased levels of IL-17 suggested a combination of Th17 and Th1 responses in HT. Both types of cells can play a crucial role in the process of cell-mediated cytotoxicity, resulting in destruction.[35] Interleukin-17, a cytokine with strong proinflammatory properties; can stimulate the production of various proinflammatory cytokines and chemokines. The presence of certain chemicals can lead to the development of an environment that promotes inflammation, thereby facilitating the progression of diseases through various mechanisms, including the formation of fibrosis.[11,29,36] The notable increase in the serum concentration of IL-17 in individuals diagnosed with HT compared to controls could possibly be linked to the autoimmune nature of HT, which demonstrates a disruption in self-tolerance and an irregular activation of the immune system, leading to the production of autoantibodies and tissue damage caused by the immune system.[37] The release of IL-17 plays a vital role in maintaining the balance of epithelial cells, triggering immediate inflammatory responses, and promoting the activation of B cells when exposed to specific triggers. This is accomplished by combining the body's natural and learned responses to protect against diseases.[38]

Conclusion

Elevated levels of anti -VCA-IgM for EBV in the patients with HT compared to the healthy controls suggest that active EBV infection may have a role in the disease's onset or progression. Also, both IFN-γ and IL-17 participate in the pathomechanisms of HT since they showed an elevated level in the serum of patients compared to the controls.

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Conflict of Interest: None

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