Original Research Article Iran J Med Microbiol. 2025; 19(3): 203-209

Category: Medical Parasitology Peer Reviewed | Open Access

10.30699/ijmm.19.3.203

Iranian Journal of Medical Microbiology | ISSN:2345-4342

CD4 and CD8 T Lymphocyte Cell Count in β-Thalassemia Major Patients Infected with Toxoplasmosis

Raghad N. Shihab[1*], Sarah Ali Saeed[2], Evan H. Sulaiman[3]

1. *Department of Cancer Research, Iraqi Center for Cancer and Medical Genetic Research, Mustansiriyah University, Baghdad, Iraq*
2. *Department of Microbiology, College of Medicine, Ibn Sina University for Medical and Pharmaceutical Sciences, Baghdad, Iraq*
3. *Department of Applied Pathological Analysis College of Science, Al-Nahrain University, Baghdad, Iraq*

ABSTRACT

Background and Aim: A collection of hereditary hemoglobin disorders known as thalassemia are typified by uneven globin-chain output due to inadequate production of at least one globin chain. *Toxoplasma (T.) gondii* parasites reside in human body as intermediate and final hosts without any symptom. Only congenitally-infected children and immunocompromised people typically exhibit severe illness of toxoplasmosis. This study aimed to determine the CD4 and CD8 count in patients with β-thalassemia major (BTM) infected with toxoplasmosis.

Materials and Methods: Ninety blood samples from BTM, BTM with toxoplasmosis, and negative control groups were selected. Among the samples, 70 were from patients with BTM, while the remaining 20 samples came from healthy people as control subjects. The IgG and IgM antibody levels against *T. gondii* were quantified using chemiluminescent microparticle immunoassay (CMIA) and CD4 and CD8 T cells count was measured using ELISA kits.

Results: The CMIA results from antibody levels demonstrated significant differences (P<0.001) between BTM patients with toxoplasmosis and negative control group. The CD4 & CD8 T cell counting of BTM patients with toxoplasmosis showed highly significant difference (P<0.0001) compared to their controls.

Conclusion: Counting CD4 and CD8 T lymphocytes in individuals with BTM who have contracted toxoplasmosis offered important information about their immune response and how to treat the illness. Tracking these subsets can help for direct clinical interventions and enhance the patients' outcomes, especially when chronic infection and immunological fatigue are involved.

Keywords: β-thalassemia Major, CD4, CD8, *Toxoplasma (T.) gondii*

Received: 2025/05/23; **Accepted**: 2025/08/03; **Published Online:** 2025/08/18;

Corresponding Information: **Raghad N. Shihab**, *Department of Cancer Research, Iraqi Center for Cancer and Medical Genetic Research, Mustansiriyah University, Baghdad, Iraq* & Email: raghad.shihab@uomustansiriyah.edu.iq

1. Introduction

The most common genetic hemoglobinopathy worldwide is β-thalassemia. It is brought on by a decrease in or lack of formation of the β-globin chain, which normally makes up a percentage of adult hemoglobin (HbA, which is α2β2) **(1, 2)**. Globally, thalassemia is the most prevalent monogenic disorder. In the most severe situations, thalassemia patients require frequent blood transfusions due to severe anemia **(3)**. Erythroid precursors in bone marrow die early and undergo inefficient erythropoiesis due to excessive and precipitated unbound α globin chains. There are either no β globin chain (β0) or reduced ones (β+).

The type of mutation at chromosome 11 in β globin gene determines the extent of globin chain reduction. Insoluble α globin chains cause membrane damage to the peripheral erythrocytes. This causes peripheral hemolysis, which is less noticeable in thalassemia major than in thalassemia intermediate but is a contributing factor to anemia. Extended, severe anemia, extramedullary erythropoiesis, and hepatosplenomegaly are caused by the enhanced erythropoietic drive. Anemia increases the synthesis of erythropoietin, which causes bone marrow to grow up to 25–30 times more than usual. This strong but ineffective enlargement leads to distinctive bone deformities **(4, 5)**. Between 50,000 and 100,000 children are estimated to die from β-thalassemia every year, with 80% of these deaths occurring in developing nations; 300,000 to 500,000 newborns are estimated to have severe hemoglobin anomalies annually **(6)**, and patients with thalassemia disease have been found with a wide range of immunological abnormalities **(7)**.

Toxoplasma (T.) gondii is responsible for the zoonotic parasitic disease called toxoplasmosis. It has worldwide distribution and is one of the most prevalent infectious agents in Iraq **(8, 9)**.

One of the factors contributing to the less successful recovery of these patients from infection is weakened innate immune system, and these variations in both quantity and functionality impact multiple components of the immunological reaction. A group of patients demonstrated low-grade systemic inflammatory condition, as evidenced by the elevated total leukocyte, neutrophil, and lymphocyte counts, as well as an altered innate immune cytokine profile **(10, 11)**. The imbalance in CD4 and CD8 T cell subgroups functionality in β-thalassemia patients may be a factor in their increased vulnerability to infections and immunological dysregulation **(12)**. Increased IgG, IgM, and IgA immunoglobulin levels are indicative of decreased immunoglobulin secretion. People with thalassemia have also shown inadequate phagocytosis and chemotaxis. Last but not least, research has shown that lower levels of C3 and C4 complement proteins are indicative of diminished opsonization, granulocyte phagocytosis, and suppressed complement system activity **(13, 14)**. This study was designed to estimate the levels of CD4 and CD8 in the patients with β-thalassemia major infected with toxoplasmosis.

2. Materials and Methods

2.1 Study Design and Sampling

This research was conducted in Baghdad, Iraq visiting the AL-karama Dialysis Center from October 2024 until the end of December 2024. Blood samples were taken from 70 patients with β-thalassemia major after they were diagnosed by the specialized doctors, and 20 healthy individuals who did not suffer from any chronic disease. Venous blood (5 ml) was extracted from the dialysis patients' connections. The blood samples were centrifuged for 10 min at 3000 g. Plasma was separated and kept at -20°C for further immunological and physiological testing. The inclusion criteria included: Patients with β-thalassemia major and infected with *T. gondii*, aged 3-45 years, and also no other chronic disease or complication. The exclusion criteria included: Chronic diseases such as diabetes, hypertension, chronic kidney disease, and arthritis. Unconscious patients or those who were in coma, and the patients with special diet were also excluded from the study. The full consent was obtained from the patients. Ethics of the research highlighted the agreement with the patient that the members of the research team would not share any information with parties other than responsible researchers.

2.2 *Toxoplasma gondii* IgG & IgM Antibodies Detection

The serological diagnosis of toxoplasmosis was conducted through automated quantitative tests. Automated techniques have several advantages: they are adapted for the routine analysis of the large samples and produce quantitative and reproducible IgG and IgM levels, especially in architectural techniques, with excellent specificity for IgG and excellent sensitivity for IgM. The ARCHITECT Toxo IgG and IgM assay is a fully automated two-step chemiluminescent immunoassay (CMIA) designed to quantify IgG or IgM antibodies against *T. gondii*. The test is based on the World Health Organization (WHO) international standard (01-600) for antibody detection against toxoplasmosis. The IgM and IgG test kits (Abbott GmbH, Germany) were used to measure IgM

and IgG levels according to the manufacturer's instructions.

2.3 CD4 and CD8 Immunological Markers Measurement

All samples were collected in anticoagulant agent citrated tubes. After incubation at room temperature for 10 to 20 min, the tubes were centrifuged for 20 min at 2,000 to 3,000 g. The supernatant was collected as plasma from the miscellaneous serum. The ELISA kit (Sunlong Biotech, China) based on Sandwich-ELISA protocol was used to evaluate CD4 and CD8 markers. The Micro-ELISA strip plate provided in the kit was pre-coated with CD4 or CD8 antibodies. The standards were tested along with samples combined with specific antibodies. Well-constructed HCV-conjugated antibodies specific for CD4 and CD8 were added to each strip and incubated. The unbound substances were washed away. TMB substrate was added to each well and optical density (OD) was measured spectrophotometrically at 450 nm wavelength. The OD is proportional to CD4 and CD8 concentrations. The concentration of CD4 and CD8 in the samples was calculated by comparing the OD of the samples with the standard curve **(15)**.

2.4 Statistical Analysis

Statistical analysis was performed using SPSS version 26 (SPSS Inc., Chicago, Illinois, USA) **(16)**. The analysis of variance (ANOVA) was performed as a crossover study involving three groups. Data were classified according to the *Toxoplasma* IgG IgM antibodies, and CD4 and CD8 counts. The least significant difference (LSD) post-hoc test was used to determine the significant levels between groups. P values less than 0.001 were considered statistically significant.

3. Results

The results of *T. gondii* antibodies detection revealed significant differences between negative control groups in IgM (0.04±0.01 U/L) and IgG (0.51±0.31 U/L) and the groups of BTM patients with toxoplasmosis in both cases of IgM (0.84±0.21) and IgG (60.25±9.18) detection. Furthermore, no significant differences were observed between BTM group and negative control either in IgM (0.27±0.03) or IgG (2.21±0.02) cases. Data for IgM and IgG detection are shown in Tables 1 and 2, respectively.

We also compared the immunological status of BTM patients with toxoplasmosis to that of healthy individuals by examining certain immune and physiological indicators; CD4 and CD8 T cells count. A comparison was conducted on CD4 T cell count between healthy controls and BTM patients with toxoplasmosis. The results demonstrated highly significant difference between the patients and healthy group (*P*=0.0001), with CD4 T cell count of the BTM patients with toxoplasmosis being 530.63±84.15 compared to the control (804.62±1.71) (Table 3).

The CD8 T cell count was also compared between BTM patients with toxoplasmosis and healthy control group. The results are displayed in Table 4 and show a highly significant difference (*P*<0.0001) between the healthy group and BTM patients with toxoplasmosis. The CD8 T cell counts were 870.67±1.25 compared to the control (597.78±3.96).

Table 1. *Toxoplasma gondii* IgM in the studied groups.

Parameter	Groups	Concentration (Mean ± S.E)	LSD	P-Value
IgM (U/L)	Negative control (-ve)	0.04±0.01	14 (40.0)	*P*<0.001**
	BTM	0.27±0.03		
	BTM with toxoplasmosis	0.84±0.21 a		

** Highly significant difference, a significant difference vs. negative control

Table 2. *Toxoplasma gondii* IgG in the studied groups.

Parameter	Groups	Concentration (Mean ± S.E)	LSD	P-Value
IgG (U/L)	Negative control (-ve)	0.51±0.31	15.03	*P*<0.001**
	BTM	2.21±0.02		
	BTM with toxoplasmosis	60.25±9.18 a		

** Highly significant difference, a significant difference vs. negative control, b vs. positive control, c vs. patients

Table 3. Concentration of CD4 in the studied groups.

Groups	CD4 (Mean ± S.E)	LSD	P-Value
Negative control (-ve)	804.62±1.71	145.12	*P*=0.0001**
BTM	594.23±3.19 a		
BTM with toxoplasmosis	530.63±84.15 ab		

** Highly significant difference, a significant difference vs. negative control, b vs. positive control, c vs. patients

Table 4. Concentration of CD8 in the studied groups.

Groups	CD4 (Mean ± S.E)	LSD	P-Value
Negative control (-ve)	597.78±3.96	12.09	*P*<0.0001**
BTM	710.33±1.76 ab		
BTM with toxoplasmosis	870.67±1.25 abc		

** Highly significant difference, a significant difference vs. negative control, b vs. positive control, c vs. patients

4. Discussion

Toxoplasma gondii is often regarded as one of the most successful parasites due to its widespread distribution, extensive range of host species, and high prevalence rates globally, leading to toxoplasmosis, an opportunistic illness that can cause significant damages **(17, 18)**.

According to study of Abd El-Latif et al **(19)**, Egyptian thalassemia patients were positive for anti-*Toxoplasma* IgG and IgM antibodies at 10% and 2%, respectively.

The current study aligns with the research conducted by Hanifehpour, Samsam Shariat **(20)** that showed 51.9 % (122/235) of the patients with BTM tested seropositive for anti-*Toxoplasma* IgG, in contrast to 34.8% (82/235) of the healthy individuals. However, the *Toxoplasma* IgG prevalence in this study was not consistent with anti-toxoplasmosis seroprevalence reported by study Dabirzadeh et al **(21)**, which showed 26.3% (29/110) of the control group and 13.6% (15/110) of thalassemia patients in Iran as seropositive for *Toxoplasma* IgG antibody. Immunologic abnormalities, including non-specific immune response, altered cytokine production, and changed lymphocyte subsets, have been demonstrated in BTM patients **(22)**. Although the exact cause of these illnesses is uncertain, potential factors may include iron overload, frequent blood transfusions, allogeneic stimulation, and iron chelation therapy **(23, 24)**.

There are three main categories into which T cells are generally divided: CD8, CD4, and Regulatory T cells (Tregs) with pro-inflammatory and anti-inflammatory functions. Pro-inflammatory CD8 T cells have the capacity to induce cytotoxicity and are implicated in the immune system response to cancer, viral infection, and metastatic cells **(25)**. In addition to

controlling inflammatory environment, CD4 T helper (Th) cells foster the creation of antibodies, activate immunologic memory, and regulate innate immunity. Tregs, anti-inflammatory CD4 cells, lower inflammatory responses, increase immunological tolerance, and regulate immune responses to avoid autoimmunity **(26)**.

In the Rakhmanova et al **(27)** investigation, the levels of ferritin, IL-6, IFN-β, and immunological markers: CD4, CD8, CD3, and CD16 were examined in 200 participants aged 1 to 27 decades. The number of adult patients was not released. Iron overload is the main cause of immunological deficiency in β-thalassemia cases, according to several studies. Reduced phagocytosis by the monocyte-macrophage system, modified T-lymphocyte subsets (represented by upregulation of CD8 and downregulation of CD4), impaired immunoglobulin secretion, and compromised complement system function (hemochromatosis, thalassemia) are the immune system abnormalities linked to the conditions involving elevated iron load **(27)**.

Iron overload is a side effect of both disease and its therapy, and it is believed to be a major contributing factor to the immunological insufficiency in BTM, according to the research by Ehsanipour, Faranoush **(28)**, an overabundance of iron may negatively affect the immune system equilibrium since iron and its protein constituents are known to be directly involved in immune regulatory mechanisms.

CD4 T cells are necessary for T lymphocyte cytotoxicity, CD8 response maintenance, and exhaustion prevention. The main immune system component that eradicates infections and malignant cells are CD8 T cells **(29)**. Major Histocompatibility Complex Class-1 (MHC-1) molecules on the surface of antigen-presenting cells (APCs) and target cells are encountered by CD8 T lymphocytes. They display antigenic peptide fragments made by proteasomal degradation of cytoplasmic proteins connected to the appropriate binding grooves **(30, 31)**. After engaging with an APC or a target cell, CD8 cells stick to the surface and move across to find MHC-antigen-peptide complexes. Direct contact and cell movement are required to transform mechanical energy into biomechanical signals that trigger the CD8 T-cell receptor (TCR) complex **(31, 32)**. Iron overload in BTM patients induces changes in neutrophil subpopulations (increased aged, immature, and low-density neutrophils), which might alter the immune responses, partly through T cell suppression. Due to possible immune suppression caused by iron overload, effective iron chelation is encouraged. Understanding of neutrophil heterogeneity and functional plasticity in β-thalassemia may develop new therapeutic approaches in future **(33)**.

Thalassemia major patients showed higher levels of CD8 expression. There was a statistically significant difference in the CD8 level between the groups under investigation. The mean value of CD8 was higher in the patients who were frequently dialyzed without a filter than in the patients who were frequently dialyzed with a filter or who that were not frequently dialyzed. Several antigenic stimuli during blood transfusion are responsible for this observation **(34)**.

5. Conclusion

Assessing the CD4 and CD8 T lymphocytes counts in individuals with β-thalassemia major who have contracted toxoplasmosis offers important information about their immune response and how to treat the illness. Keeping an eye on these subsets can help direct treatment interventions and enhance the patients' outcomes, especially when chronic infection and immunological depletion are involved.

6. Declarations

6.1 Acknowledgment

The authors thank all individuals who participated in the research, whether patients or control group.

6.2 Ethical Considerations

This research was approved by the Ethics Committee of the Mustansiriyah University, Iraqi Center for Cancer and Medical Genetic Research, Baghdad, Iraq. No.: ICCMGR.REC.2025/01.

6.3 Authors' Contributions

Raghad N. Shihab: conceived and designed the experiments, followed up on the patients' cases, asked them to conduct experiments on themselves, collected laboratory test results, wrote the paper. Sarah Ali Saeed: writing-review, analyzed laboratory data. Evan H. Sulaiman: analyzed statistics. All authors have read and approved the manuscript.

6.4 Conflict of Interests

The authors declare no conflict of interest.

6.5 Financial Support and Sponsorship

The authors did not receive financial support for conducting this study.

6.6 Using Artificial Intelligence Tools (AI Tools)

Not applicable.

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