

The Effect of *Toxoplasma gondii* Infection on Serotonin (5-HT) levels and their impact on GABAergic Activity

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Abstract: The present work is directed towards evaluating the alterations of serotonin and GABA concentration levels due to *Toxoplasma gondii* infection. **Methods:** For this, a total of 120 subjects were selected, among whom 60 were infected patients and 60 were normal controls. ELISA was employed for determining the serum levels of these two components. **Results :** Based on the results, marked neuroendocrine alterations were observed in infected patients. Serum levels of serotonin were observed to be significantly reduced in infected patients, i.e., 0.5441 ± 0.039 ng/mL, whereas these levels were high in normal controls, i.e., 1.500 ± 0.102 ng/mL. $p < 0.0001$. In addition, there was a significant reduction of GABA levels observed in infected patients when compared with normal controls (1.530 ± 0.099 pg/L and 6.125 ± 0.156 pg/L, $p < 0.0001$, respectively). A very weak and insignificant relationship of serotonin and GABA concentration levels was observed in infected patients ($r^2 = 0.001$). **Conclusion:** It can be highlighted from the above findings that alterations of serotonin and GABA concentration levels in infected patients lead to a marked reduction of two of the important inhibitory components of neurotransmitters. These two inhibitory components could lead to an imbalance towards an excitatory state of the neural system and explain neurobehavioral and psychological alterations observed in patients suffering from chronic toxoplasmosis.

Keywords: *Toxoplasma gondii*, Toxoplasmosis, Serotonin, Gamma-aminobutyric acid (GABA), Neurotransmitters.

1. Introduction

Toxoplasma gondii is an obligate intracellular protozoan parasite that has gained considerable attention for its unique tropism towards neural tissue. Following primary infection, which is typically asymptomatic in immunocompetent persons, the pathogen establishes latent tissue cysts, predominantly in the central nervous system (CNS) and skeletal muscles, leading to a chronic infection that lasts a lifetime [1]. The persistence of this infection in the CNS, however, has not been without consequences, with a growing body of evidence

emerging that associates chronic toxoplasmosis with a range of neuropsychiatric and behavioral disorders, including schizophrenia, mood disorders, and behavioral changes [2,3]. The mechanisms involved in this neuropsychiatric symptomatology are multifactorial and intricate, and the most prevailing theory is based on the parasite's ability to slightly alter the host's neurochemical environment. This low-grade level of neuroinflammation can significantly affect the production, release, and metabolism of important neurotransmitters in the host brain. Amongst them, the serotonergic and GABAergic systems are of prime importance due to their basic role

in maintaining emotional and neurological homeostasis in the host body [4, 5]. Serotonin (5-hydroxytryptamine, 5-HT) is a monoamine neurotransmitter involved in regulating a broad range of brain functions. The dysfunction of the serotonergic system is considered a key factor in the pathophysiology of major depressive disorder, anxiety disorders, and other psychiatric disorders [6, 7]. Gamma-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter of the mammalian central nervous system. GABA is crucial for balancing excitatory neurotransmission via glutamate and controlling neuronal excitability, stress responses, and preventing hyper-excitability of neurons. GABA dysfunction is linked with anxiety disorders, depression, schizophrenia, and epilepsy [8, 9]. Recent findings suggest that *T. gondii* infection affects these systems through different mechanisms. The parasites' cysts are found in brain cells such as neurons and glial cells and could interfere with their function. The neuroinflammation caused by *T. gondii* could also modulate the activity of crucial enzymes such as tryptophan hydroxylase for serotonin synthesis and glutamic acid decarboxylase (GAD) for GABA synthesis and could also modulate the activity of their respective receptors [10,11]. The objectives of this study are to quantitatively evaluate the serum levels of serotonin and GABA in patients infected with *T. gondii* compared with healthy individuals. The secondary objective of this study is to evaluate the possible relationship between these two inhibitory neurotransmitter systems and its potential role in explaining the complex neurochemical imbalance of toxoplasmosis [12].

2. Methodology

Study Design and Participants: The present case-control study was carried out at Al-Zahraa Teaching Hospital and some private medical laboratories located at Al-Najaf Governorate, Iraq, from September to December 2025. The total number of participants included in the present study was 120, and the participants were equally distributed into two groups: 60 patients with chronic *T. gondii* infection and 60 healthy controls. The criteria for chronic *T. gondii* infection were the presence of anti-Toxoplasma IgG antibodies with negative IgM antibodies. The exclusion criteria for all participants included a history of neuropsychiatric disorders, antidepressant and anxiolytic medication,

chronic conditions such as diabetes and renal failure, and pregnancy.

Serological Confirmation: Venous blood samples (5 mL) were drawn from all the participants. Sera were separated by centrifugation and stored at -20°C until analysis. The serological status of the patients with respect to *T. gondii* infection was determined using the VIDAS TOXO IgG II and IgM II ELFA kits (bioMérieux, France), as per the instructions provided in the kit.

Serotonin Quantification: The concentration of serotonin (5-HT) in the serum was determined using a commercially available Human Serotonin ELISA Kit (Bioassay Technology Laboratory, China). Briefly, 40 µL of the serum sample or 50 µL of standard was added to pre-coated microtiter wells. Then, 10 µL of anti-5-HT antibody and 50 µL of streptavidin-HRP conjugate were added to each well, except the blank wells. The plate was incubated at 37°C for 60 minutes and was subsequently washed five times. Then, 50 µL of substrate solution A and 50 µL of substrate solution B were added to each well and incubated at 37°C in the dark for 10 minutes. Then, 50 µL of Stop Solution was added to each well, and the plate was read immediately at 450 nm using a microplate reader.

GABA Quantification: The concentration of GABA in serum was estimated using a Human GABA ELISA Kit (Bioassay Technology Laboratory, China). The steps involved in this technique are as follows: 50 µL of standard or sample solution was added to the wells, and then 100 µL of Enzyme Conjugate solution was added and incubated for 60 minutes at room temperature. After incubation, four washes were carried out, followed by the addition of 50 µL of Substrate A and 50 µL of Substrate B solutions, and incubation at room temperature in the dark for 15 minutes. The reaction was terminated by adding 50 µL of Stop Solution, and then the results were read at 450 nm.

Statistical Analysis: Statistical analysis was carried out using GraphPad Prism (version 5.04 for Windows, GraphPad Software Inc., USA). The results are presented as mean values and standard error of the mean (SEM). The mean values of serotonin and GABA in the patient and control groups were compared using the unpaired

Student's t-test. The correlation between serotonin and GABA in the infected patient group was determined using Pearson's correlation coefficient (r). The results were considered significant at $p < 0.05$.

A standard curve should be constructed for each assay as shown in Figures 1 and 2.

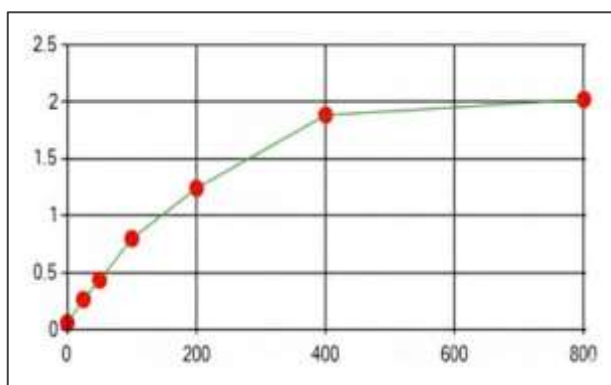


Fig 1: Standard Curve of Human Serotonin (ng/mL).

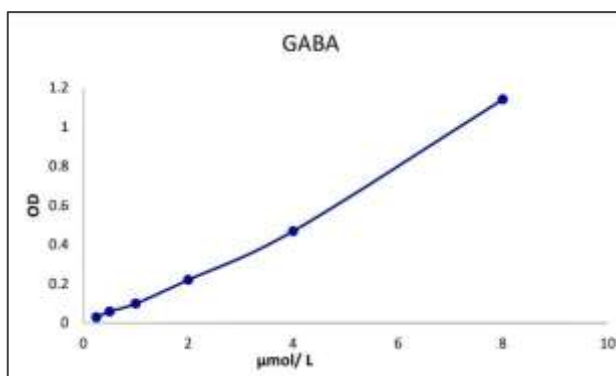


Fig 2. Standard Curve of Human GABA μl/ml.

3. Results and discussion

Demographic and Baseline Characteristics: The present study consisted of 60 patients with chronic toxoplasmosis and 60 healthy controls. The demographic and baseline characteristics of the cases and controls were comparable with respect to age and sex distribution. The mean age of the patient group and the control group were 36.5 ± 8.2 and 35.8 ± 7.9 years, respectively ($p = 0.63$). Both the patient and control groups consisted of 35 females (58.3%) and 25 males (41.7%).

Serotonin Levels: The present study found a highly significant decrease in the serum levels of serotonin among the *T. gondii*-infected patients when compared with the healthy control group. As depicted in Figure (1) and Table 2, the mean concentration of serotonin among the *T. gondii* patients was found to be 0.5441 ± 0.039 ng/mL, which is approximately one-third of the mean concentration of serotonin among the healthy controls, i.e., 1.500 ± 0.102 ng/mL ($p < 0.0001$) as shown in Figure 3.

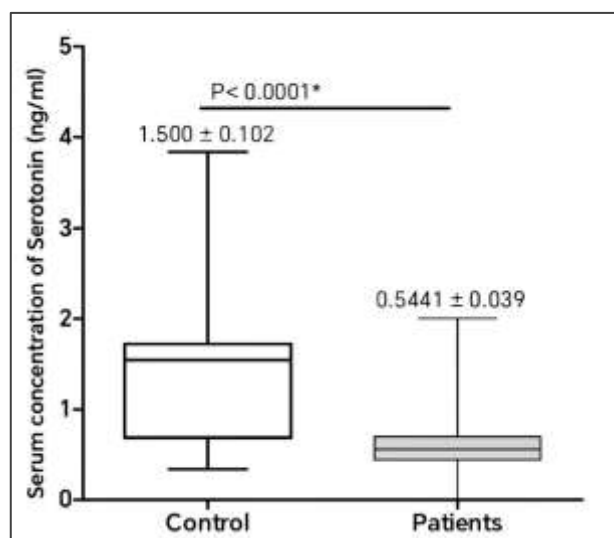


Fig.3: Concentration of human Serotonin (ng/ml).

GABA Levels: Similarly, serum GABA levels were found to be significantly low in the patient group. The mean concentration of GABA was found to be 1.530 ± 0.099 pg/L for infected patients, whereas for the control group, it was 6.125 ± 0.156 pg/L ($p < 0.0001$).

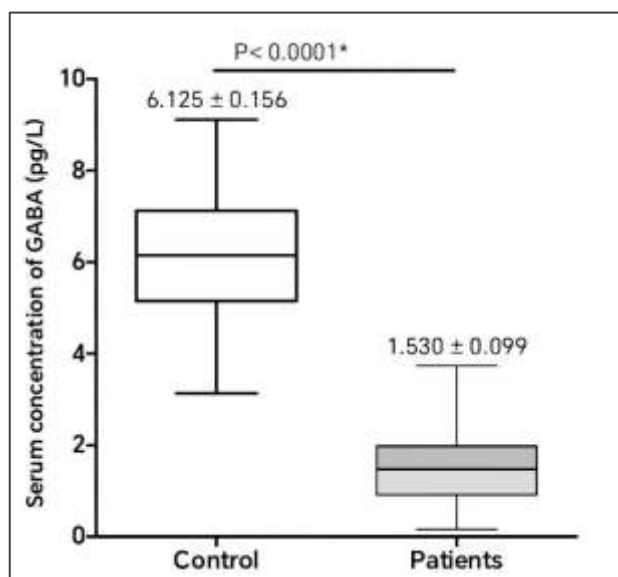


Fig 4: Concentration of human GABA(pg/L).

Correlation between Serotonin and GABA:

Pearson's correlation coefficient was calculated for infected patients, and it was observed that there was a very weak and statistically non-significant relationship between the levels of these two neurotransmitters, i.e., serotonin and GABA ($r^2 = 0.001$, $p = 0.81$), and the regression line showed a negligible positive relationship between them, indicating that these two neurotransmitters reduce independently of each other. As indicated in Figure 5.

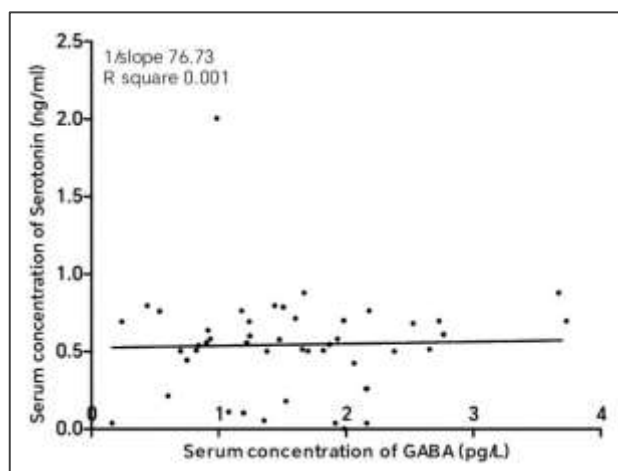


Fig 5: The Correlation between Serum Concentrations of Serotonin and Level of GABA in patients suffering from

T. gondii infection

The results of this study present conclusive evidence for the first time that chronic infection with *T. gondii* is linked with significant and simultaneous suppression of two major inhibitory neurotransmitter systems in the body, namely, the serotonergic and GABA neurotransmitter systems. The significant reduction in the concentration of serotonin and GABA in the serum of infected patients compared to healthy controls indicates a significant neurochemical imbalance, which may cause behavioral and psychiatric abnormalities commonly observed in patients suffering from chronic toxoplasmosis [13, 14]. The significant reduction in the concentration of serotonin in the serum of infected patients compared to healthy controls is also in accordance with the known fact that *T. gondii* infection can cause neuroinflammation in the body. The pro-inflammatory cytokines, such as interferon-gamma (IFN- γ) and tumor necrosis factor-alpha (TNF- α), which are elevated in the body during chronic *T. gondii* infection, can induce the activation of the enzyme indoleamine 2,3-dioxygenase (IDO). The activation of this enzyme can cause a reduction in the availability of serotonin in the body by shunting the essential amino acid, tryptophan, away from the production of serotonin and into the kynurenine pathway [15, 16]. The concomitant and parallel reduction of GABA levels is also of equal importance. GABA is produced from glutamate by GAD65 and GAD67 enzymes and is known as the primary inhibitory neurotransmitter of the brain. The observed reduction of serum GABA could be attributed to a defect in its biosynthesis or increased metabolism. The neuroinflammation caused by *T. gondii* could result in excitotoxicity and oxidative stress, leading to dysfunction of GABAergic interneurons or reduced activity of GAD enzymes. This is of significant interest because reduced GABAergic activity is a key component of the neurochemistry of anxiety disorders, depression, and schizophrenia, all of which are linked to toxoplasmosis [17, 18]. The parallel reduction of 5-HT and GABA levels represents a "dual hit" on the brain's inhibitory neurotransmitter systems. The state of reduced serotonergic and GABAergic activity would logically result in a state of neurochemical imbalance favoring excitation. This imbalance of neurotransmitters would result in increased neuronal excitability and a lowered threshold for stress and neuropsychiatric disorders such

as anxiety and mood disorders. This neurochemistry represents a mechanistic explanation of the epidemiological evidence linking *T. gondii* seropositivity with increased risk of neuropsychiatric disorders [19, 20].

One of the fascinating and new aspects of our research is the absence of a significant relationship between serotonin and GABA levels in infected patients. This very low and insignificant relationship ($r^2 = 0.001$) suggests that the reduction of these two neurotransmitters is not caused by a single and tightly regulated process of failure. This observation rather suggests that *T. gondii* infection affects these two neurotransmitter systems separately and through distinct pathological mechanisms. For example, the reduction of serotonin might be caused by IDO-mediated tryptophan metabolism, whereas the reduction of GABA might result from more direct inflammatory damage of specific populations of interneurons and excitotoxicity. This observation underlines the complexity of *T. gondii*-induced effects on the host's central nervous system and suggests that therapeutic approaches might need to address multiple neurotransmitter systems simultaneously [21, 22]. It is also important to note the limitation of this study. It is true that measuring the concentration of neurotransmitters in the serum is not the same as measuring them in the specific synapse in the brain, although this is not completely accurate, as research has indicated some correlation, especially in the presence of systemic inflammation. Future research is needed to investigate the exact mechanism by which *T. gondii* causes these neurochemical changes, using cerebrospinal fluid and animal models [23].

Conclusion

This study showed that *T. gondii* infection caused a marked reduction of serum levels of serotonin and GABA, suggesting a marked suppression of major inhibitory neurotransmitter systems. Such neurochemical imbalance, defined by decreased levels of inhibitory tone, is likely responsible for the mood and behavioral changes observed during chronic toxoplasmosis. The poor relationship between decreased levels of serotonin and GABA suggests that these neurochemical losses might be mediated by different pathological mechanisms rather than a similar one. These findings highlight the

intricate effects of *T. gondii* infection on host neurochemistry and emphasize the need for more research on neuro-immune interactions responsible for infection-induced neuropsychiatric syndromes.

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Author's Contributions

Amshah Fakhri Abbas Almosawi assisted in the study design, sample collection, laboratory work, data analysis, and manuscript preparation. Dr. Sukayna Jabbar Mushattat supervised the study and helped in the study design, data analysis, and manuscript revision.

Ethics

This research was approved by the ethical committee of the Faculty of Science, University of Kufa (Approval Number: /2026). Written informed consent was obtained from all participants who were included in the study.

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