Latent *Toxoplasma*, schizophrenia, and depression: a case study in urban Ecuador

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Abstract

Background:

In recent years several research projects around the world have aimed to determine a possible infectious origin of schizophrenia, where a higher prevalence of Immunoglobulin G antibodies against *Toxoplasma* has been observed in these patients. Differences in symptoms between infected and non-infected patients have also been described. Finding the link between *Toxoplasma* and Schizophrenia is a complex challenge that requires further research which will allow better treatment options, symptoms improvement and quality of life.

Methods:

Search of differences on symptomatology was performed by studying 104 patients diagnosed with schizophrenia from the Institute of Neurosciences of the city of Guayaquil, who underwent ELISA testing to detect Immunoglobulin G against *Toxoplasma gondii*.

Results:

Of these 104 samples, 90 were positive, obtaining an 86.5% prevalence. Thirteen symptoms were taken from clinical notes, where the infection with *Toxoplasma gondii* was found to be a protective factor for schizophrenia patients against depression

Conclusion:

These findings add evidence to previous reports that latent *Toxoplasma* may protect against depression in patients with schizophrenia.

1. Background

Toxoplasma gondii is an obligate intracellular parasitic protozoan that affects over a third of the world population. Low seroprevalence has been reported in North America, Northern Europe and South East Asia while high prevalence has been observed in South America and in tropical African countries (1).

T. gondii was first described in 1908, when it was isolated from rodents at the Pasteur Institute in Tunis. It is transmitted by the ingestion of water or vegetables contaminated with sporulated oocysts, ingestion of raw or undercooked meat containing cysts, manipulation of contaminated cat feces, vertical transmission from an infected mother to her child, blood transfusion and organ transplant (2) and it persists in the hosts for the rest of their lives, as bradyzoites in tissue cysts located in the central nervous system, lungs, liver, kidneys, eyes, muscles, reproductive organs and semen (3).

The clinical presentation of the infection with *Toxoplasma gondii* varies widely depending on the genotype (type I isolates are highly virulent while type II and III are avirulent strains), the immunological

status of the host and the mode of transmission (4)(5).

On the other hand, schizophrenia is a complex neuropsychiatric disorder that affects 1% of the world population and the 9th most common cause of disability all over the world (6). Its etiology remains unknown; however it is associated with genetic and environmental factors like exposure to pathogens, physical stress and fetal starvation during pregnancy (7). Any of these exposures could lead to altered behavior patterns and cognitive functions that will end in neuropsychiatric consequences (8) such as irreversible neurological lesions leading to neuronal dysfunction, behavior problems, mental retardation, learning difficulties, or mood disorders.

Schizophrenia clinical manifestations include visual or auditory hallucinations which are the most characteristic among the clinical spectrum; these have been described as positive, negative, affective and cognitive symptoms (1,9).

For half a century, a possible relationship between schizophrenia and *Toxoplasma gondii* has been studied, leading to encouraging results regarding the possibility that the infection with the parasite could lead, among other factors, to the psychiatric disorder. The infection has also been related to a worsen clinical course (1,2,4,10) relationship which has not been as much described and studied as the foremost but could shed more light in this topic. The full elucidation of these associations will promote specific antimicrobial treatments to be added to current symptomatic (or antipsychotic) treatments leading to a preventive and curative approach to the disease as they would act on known and treatable etiologic factors (11). Therefore, the aim of this study is to determine the differences in psychopathology between *Toxoplasma*-related and *Toxoplasma*-unrelated schizophrenia from a group of patients from the Institute of Neurosciences of the city of Guayaquil.

2. Methods

The study was performed at the Neuroscience Institute of the city of Guayaquil (INC), Ecuador, which is the largest psychiatric hospital of the country. From all the 368 INC inpatients, 104 patients were chosen following inclusion and exclusion criteria; the first were age 18–85, diagnosis of schizophrenia as per the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria and age at diagnosis of 12–40 years old. Exclusion criteria were neurological diseases, denial of participation in the study and immunodepression.

Ethic approval was obtained prospectively through the ethics committee of the Kennedy Clinic (CGVD-2016-0666) and full funds were provided by the Investigation Center of the Universidad de Especialidades Espiritu Santo (UEES). The 104 patients were older than 18 years old and provided written informed consent, after thorough explanation of the study to them. The study was carried out in concordance with the latest version of the Declaration of Helsinki.

All patients in the study were born and raised in Ecuador, did not show laboratory abnormalities for the last 30 days nor clinic of other medical diseases, and all had been under antipsychotic medication for the

last 5 years minimum.

Blood samples were taken, by a trained nurse, after obtaining a written informed consent of all the 104 patients following a verbal and written explanation of the study. The samples were encoded to preserve the confidentiality of the patients, thereafter the samples were frozen and taken to the laboratory. The Immunoglobulin G (IgG) seropositivity for *Toxoplasma gondii* were determined by a private laboratory through a commercially available quantitative enzyme-linked immunosorbent assay (ELISA) kit (Vircell microbiologists), in which the test was performed according to the manufacturer's instructions.

The clinical characteristics of the patients were obtained from the patients' clinical records, these included the Positive and negative symptoms scale (PANSS), which was previously carried out by the psychiatrists of the hospitalization wards.

Statistical significance between *Toxoplasma gondii* IgG seropositivity and schizophrenia, gender, schizophrenia subtype and clinical symptoms were determined with Pearson's chi-squared test (χ^2) through Statistical Package for the Social Sciences (SPSS) Statistics (23.0 version).

3. Results

The final sample included 104 patients (84 men and 20 women) with schizophrenia, from which 90 were positive for *Toxoplasma* IgG on serum, this corresponds to a prevalence of 87%. There was no significant difference in the prevalence of seropositivity between genders ($p = 0.61$, CI 95% = 0.14–3.25), in which 72 men (85.7%) and 18 (90%) women were *Toxoplasma*-infected. The range of age was from 29 to 79, with a mean of 58.4. All the patients included in this study were divided according to their type of schizophrenia and based on the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD). 33 (31.7%) patients were diagnosed with paranoid schizophrenia, 8 (7.7%) patients had the diagnosis of hebephrenic schizophrenia, 32 (30.76%) were classified as undifferentiated schizophrenia, 22 (21.15%) patients suffered from post-schizophrenic depression, 6 (5.76%) were classified as simple schizophrenia, and 3 (2.88%) as unspecified schizophrenia (Table 1).

Table 1 also shows the clinical characteristics presented by the patients included in this study. It is important to remember that certain characteristics may overlap between patients, as schizophrenia is a complex disease with multiple manifestations. The most common characteristics were irritability, cognitive deterioration, visual hallucinations and language disorganization.

Table 2 shows the subtype of schizophrenia presented by the patients and the relation the to the presence of IgG antibodies for *T. gondii*, showing there was no significance related to the subtype of schizophrenia between the infected and the non-infected patients.

Clinical characteristics and symptoms related to the presence of *Toxoplasma* IgG showed no significant difference between the infected and non-infected patients in most of the items (Table 3). However,

depression was found to be negatively associated to *Toxoplasma*, although it didn't survive multiple tests (OR: 0.278, CI₉₅: 0.072–1.07) (Table 4).

Table 1
Clinical and biological characteristics of patients included in this study.

Variable	Level	n	%
Gender	Male	20	19.2
	Female	84	80.8
Schizophrenia type	Paranoid	33	31.7
	Hebephrenic	8	7.7
	Undifferentiated	32	30.76
	Residual schizophrenia	22	21.15
	Simple schizophrenia	6	5.76
	Unspecified schizophrenia	3	2.88

Table 2
Schizophrenia type and its relation to *Toxoplasma* IgG

Schizophrenia type	<i>Toxoplasma</i> IgG	N	P	CI 95%
Paranoid	Positive	27	0.34	0.18–1.81
	Negative	6		
Hebephrenic	Positive	7	0.93	0.13–9.65
	Negative	1		
Undifferentiated	Positive	30	0.15	0.6-14.27
	Negative	2		
Residual	Positive	18	0.46	0.18–2.22
	Negative	4		
Simple	Positive	5	0.81	0.083–7.07
	Negative	1		
Unspecified	Positive	3	0.49	0.18–2.21
	Negative	0		

Table 3
Clinical characteristic and its relation to the presence of *Toxoplasma* IgG

Variable	<i>Toxoplasma</i> IgG	N	P	CI 95%
Visual hallucinations	Positive	40	0.698	0.26–2.46
	Negative	7		
Delusional ideas	Positive	35	0.82	0.355-3.7
	Negative	5		
Language disorganization	Positive	41	0.49	0.47–4.85
	Negative	5		
Memory impairment	Positive	6	0.32	0.07–2.37
	Negative	2		
Dromomania	Positive	22	0.4	0.40–9.35
	Negative	2		
Depression	Positive	9	0.051	0.07–1.07
	Negative	4		
Insomnia	Positive	34	0.24	0.58–8.6
	Negative	3		
Anxiety	Positive	13	0.5	0.15–2.25
	Negative	3		
Catatonia	Positive	2	0.31	0.03–3.49
	Negative	1		
Unsteady gait	Positive	23	0.36	0.49–9.9
	Negative	2		
Disorientation	Positive	45	0.058	0.96–14.01
	Negative	3		
Cognitive impairment	Positive	50	0.69	0.41–3.86
	Negative	7		
Irritability	Positive	53	0.9	0.34–3.36
	Negative	8		

Table 4
Clinical characteristic and their respective Odds ratio and confidence interval

Variable	Value	95% Confidence Interval	
		Lower	Upper
Visual hallucinations	0,8	0,259	2,469
Delusional ideas	1,145	0,355	3,7
Language disorganization	1,506	0,468	4,849
Memory impairment	0,429	0,077	2,371
Dromomania	1,941	0,403	9,352
Depression	0,278	0,072	1,07
Insomnia	2,226	0,58	8,552
Anxiety	0,619	0,152	2,524
Catatonia	0,295	0,25	3,493
Unsteady gait	2,06	0,428	9,901
Disorientation	3,667	0,958	14,028
Cognitive impairment	1,25	0,405	3,858
Irritability	1,074	0,344	3,355

4. Discussion

Despite of not finding any statistically significant relations between variables there are some associations found that possibly would have survived multiple tests if some limitations would not have been present, like lack of control group and population size.

One of the observations noticed is that the infection with *Toxoplasma* was found to be a protective factor for schizophrenia patients against depression (OR: 0.278, CI₉₅: 0.072–1.07). This coincides with previously published data, where this pattern was interpreted as a way of demonstrating how the infection has rather unknown specific effects on mental functions rather than a deleterious general influence on it (12–14).

On the other hand, these observations contrasts with the data obtained by Ling et al, in which they found a positive relation between suicide attempts and infection with *Toxoplasma*, which was presumed to be the consequence of an exacerbation of depression caused by the infection, the exacerbation may have been caused by proinflammatory cytokines that appear to target the infection(15). This was also

described by Kar et al, where a case of depression with poor response to treatment was found to be infected with *Toxoplasma*, the patient became responsive to antidepressants after completing with medication for the infection (16). A worse clinical course and lack of response to medication in *Toxoplasma* infected schizophrenia patients has also been reported (7), where absence of awareness of the disorder by the patient was reported to be sign of a worse clinical course.

A possible explanation of the effects of the infection on schizophrenia could be the reduction in gray matter caused by the latent infection of the parasite. The authors (17) explained that the *Toxoplasma* latent infection leads to the release of Interferon- γ (IFN) which induces the production of an enzyme key to *Toxoplasma* replication, releasing kynurenic acid as a metabolic product of said replication, which is an antagonist molecule for the glutamate *N*-methyl-D-aspartate (NMDA) receptor, which plays a key role in schizophrenia neuromodulation. This situation, in vulnerable subjects, could create a perfect harvesting environment for schizophrenia (18)..

5. Conclusion

The results obtained in this study and other past studies gives a light for continuing studying the relationship between infectious diseases and schizophrenia, which can aid to generate a more complete approach of disease improving the well-being of the schizophrenia patients. As to our knowledge there has not been any similar study carried out in South America before, thus this study aims to motivate the development of larger studies in the subject.

Abbreviations

- a. INC: Instituto de Neurociencias
- b. DSM-IV: Diagnostic and Statistical Manual of Mental Disorders IV edition
- c. UEES: Universidad de Especialidades Espíritu Santo
- d. IgG: Immunoglobulin G
- e. ELISA: enzyme-linked immunosorbent assay
- f. PANSS: Positive and negative symptoms scale
- g. SPSS: *Statistical* Package for the Social Sciences
- h. ICD: International Statistical Classification of Diseases and Related Health Problems
- i. NMDA: *N*-methyl-D-aspartate

Declarations

7.1. Ethics approval and consent to participate

Ethics approval was gained prospectively through the ethics committee of the Kennedy Clinic (CGVD-2016-0666). After thorough explanation of the study to all 104 patients, they provided written informed consent.

7.2. Consent for publication

Not applicable

7.3. Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

7.4. Competing interests

The authors declare that they have no competing interests

7.5. Funding

Funds were fully supplied by the Investigation Center of UEES which did not generate any bias regarding the design, collection, analysis, interpretation and writing of this article.

7.6. Authors' contributions

DR conceptualized and was the project administrator which lead to the production of the article, obtained permissions and funding acquisition while being a major part of writing the several drafts of the article. EL performed data curation, obtained and studied medical records at INC. JA used statistical software to analyze data obtained from the patients clinical records and validated materials and methods. LV defined the articles methodology and helped writing the original draft. MI was a major contributor in writing the original and subsequent draft while supervising data and statistical analysis. MS supervised ethical approvals and INC permissions, he was also a major part at designing methodology. FA studied references and generated background information for writing the original draft. ST supervised original and final draft while contributing to the article design and methodology. NS helped obtaining funds, permissions and contributed to final draft writing.

7.7. Acknowledgements

Not applicable.

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