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Toxoplasma gondii Infection in Patients Submitted to Liver Transplantation

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Toxoplasma gondii Infection in Patients Submitted to Liver Transplantation

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Abstract: Background: The liver has emerged as a frequent transplanted organ which can transmit T. gondii between seropositive donors and seronegative recipients. Associated with the immunosuppressive therapy of recipients, the presence of cysts in donor livers elevate the risk of severe toxoplasmosis in recipients. Objectives: The objective of the study was to verify the frequencies of positive serology in liver graft donors and their respective recipients, as well as to verify whether their clinical signs presented post-transplant are associated with the serological status of recipients. Patients and methods: All data on liver transplant recipients from 2008 to 2018 were obtained from the MVPeP electronic medical records of the Liver Transplant Service of FUNFARME/FAMERP. IgM and IgG anti-T. gondii antibody serology was investigated by chemiluminescence. According to the serological profile, four groups of recipients were assessed (G1: IgG-/IgM-; G2: IgG+/IgM-; G3: IgG+/IgM+, G4: IgG-/IgM+). Results: The numbers of recipients according to the serological profile groups were: G1: 20 (41.7%), G2: 26 (54.1%; G3: 2 (4.2%). No cases were found for G4. Post-transplant clinical manifestations such as fever without defined cause, lung nodules, headache, hepatosplenomegaly, encephalopathy and hepatitis (A, B and C) were reported in all groups. Conclusions: This study demonstrates that there is a high prevalence of T. gondii infection in liver recipients and, therefore, screening should be intensified. Furthermore, a high incidence of co-infection with hepatitis A was identified especially in patients who died in the post-transplant period.

Keywords: *Toxoplasma gondii*; solid organ transplantation; liver transplantation; infection

1. Introduction

Solid organ transplantation in humans provides an opportunity to investigate bacterial, viral and parasitic infections whose etiological agents can be transmitted through the graft [1]. Publications on this topic are common, but the frequency of infections transmitted through the graft is still underestimated compared to those not necessarily related to organ transplantation [2].

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One significant pathogen that can be transmitted through the graft is Toxoplasma gondii, an apicomplexan parasite that infects nucleated cells of warm-blooded animals [3]. Its transmission occurs through different routes, such as drinking water contaminated by oocysts, eating raw or undercooked meat, and contaminated fruits and vegetables[4,5].

Although T. gondii infection remains asymptomatic in most individuals, it can progress to different clinical forms including ocular, gestational and neurological toxoplasmosis [6]. Toxoplasmosis is rare but possibly fatal in immunocompromised patients and can cause other diseases such as encephalitis, myocarditis, pneumonia, chorioretinitis and generalized lymphadenopathy[1,7–11] .

Recipients of donor organs can suffer the reactivation of previously latent infections after transplantation due to immunosuppression [8,10–15]. Although the first report of toxoplasmosis in a liver graft recipient was published more than five decades ago, there are still few published studies that evaluated the transmission of T. gondii during this medical procedure [12,15,16]. Most reports refer to the transplantation of other organs and tissues as is demonstrated in review articles published over the last decade.[17–20]

As T. gondi infects nucleated cells, it can be assumed that the liver is a target organ of this parasite and its cysts can be transmitted from seropositive donors to seronegative recipients. Therefore, serological screening of donors and recipients before transplantation as well as chemoprophylaxis may be necessary [12].

According to Derouin et al., toxoplasmosis continues to be one of the most serious opportunistic infections after organ transplantation; affecting 75% of patients who did not receive prophylaxis the mortality rate is high in cases of late diagnosis [21]. Webb et al. reported a case of toxoplasmic chorioretinitis in a liver transplant recipient even after prophylaxis, with transmission likely to have occurred through the graft, since diagnosis by serology (a widely used method) was obtained late on, with the use of molecular methods being necessary to confirm infection. Toxoplasma infection has been shown to be a potential risk factor in the liver transplant population despite the use of trimethoprim-sulfamethoxazole (TMP/SMX) prophylaxis [22].

Given this context, the objective of the study was to verify the frequencies of positive serology in liver graft donors and their respective recipients, as well as to verify whether the clinical signs presented by the recipients post-transplant are associated with their serological status. Better knowledge of these data will allow a comparison of seroepidemiological data of the organ donor and the recipient, as well as their clinical findings and consequently, possibly provide a basis for the prevention and prophylaxis of morbidity and mortality due to toxoplasmosis in the post-transplant period.

2. Materials and Methods

Study setting

São José do Rio Preto is a city in the northwestern region of the state of São Paulo (SP) with a population of 469,173 inhabitants and a Municipal Human Development Index (MHDI) of 0.797 (UN, 2010). The municipality health service renowned both in the state of São Paulo and on the national scene for the excellent performance index of the Brazilian Unified Health System(SUS, n.d.) of 6.55. Serving 102 municipalities in the northwestern region of the state and throughout Brazil, the institution is one part of the Medicine School (FAMERP)/Hospital de Base (FUNFARME) complex that provides health care through the national healthcare system (SUS). It has been a reference center in organ and tissue transplants since 1992, in particular for liver transplants.

Study design

This retrospective study analyzed clinical and epidemiological data obtained from the MVPeP electronic medical records on liver donors and their respective recipients transplanted in the Liver Transplant Service of FUNFARME/FAMERP from 2008 to 2018.

Two inclusion criteria were used for donors and recipients of liver grafts: 1) Clinical profile - i) fever not justified by any other reason; ii) lymphadenopathy; iii) neuroinfection (meningoencephalitis and/or expansive lesion); iv) motor deficit related to a central nervous system (CNS) expansive lesion;

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v) abscess without defined causes; vi) pulmonary nodule; vii) pneumonitis (diffuse interstitial lesion); viii) visual alteration (chorioretinitis); ix) headache without defined etiology; x) hepatitis (elevation of liver enzymes) without defined etiology; xi) hepatosplenomegaly without other defined etiology; xii) encephalopathy; xiii) myocarditis; and 2) Anti-T. gondii antibodies detected by chemiluminescence (CLIA, Roche) performed as screening before the transplant procedure.

Screening according to serological status of patients

Liver transplant recipients and donors were divided into four groups according to the serological results for IgM and IgG anti-T. gondii antibodies: G1: IgG-/IgM-; G2: IgG+/IgM-; G3: IgG+/IgM+; G4: IgG-/IgM+.

Statistical analysis

The Shapiro-Wilk test was used to confirm normality of variables and the chi-square test and Student T-test were used to analyze significance using the PAST (version 2.7c) and GraphPad Instat (version 6.3) statistics programs. All variables with two-tailed p-values > 0.05 were considered significant.

3. Results

The medical records of 354 liver graft recipients transplanted at the hospital from 2008 to 2018 were revisited. Data from 48 recipients were eligible for analyses. The other records were excluded due to the lack of information on the clinical and epidemiological profiles.

The average age of the recipients was 55.3 (± 15.3) years with a median of 61.5 (Range: 21-75) years. The average age of the female recipients (n = 17) was 42.7 (± 17.0) years and of the male recipients (n = 31) it was 62.2 (±10.9) years (p-value > 0.0001).

Table 1 shows the distribution of the serological profiles of recipients for IgM and IgG anti-T. gondii antibodies, the symptoms of recipients and types of hepatitis identified as well as the occurrence or not of deaths. No recipients were found with a serological profile compatible with G4 (IgM+/IgG-).

The number of deaths observed in group G1 was higher in males (n = 7; 77.8%) than in females (n = 2; 22.2%) compared to group G2 (n = 5; 55.6% for males and n = 4; 44.4% for females) but the differences were not statistically significant (p-value = 0.334). The two recipients in G3 group were male. Of the 12 liver graft donors with available data, five (41.7%) were non-reactive for IgM and IgG and seven (58.3%) were reactive only for IgG. Of the respective graft recipients of IgG-reactive donors, two (28.6%) were non-reactive for IgM and IgG, three (42.8%) were reactive only for IgG and two (28.6%) were reactive for IgM and IgG.

Of the 20 recipients who died, four (20%) were only reactive for IgG as were their respective donors. Only one recipient who was non-reactive for both IgM and IgG anti-T. gondii antibodies received a graft from a similar non-reactive respective donor. As data from the other cases were not available for a more detailed analysis, it was not possible to prove any relationship between the donors' serological profile as a risk factor for the transmission of T. gondii cysts through grafts.

Co-infection by T. gondii with hepatitis was observed in 39 recipients; this was greater for hepatitis A (n = 23; 59.0%) than for hepatitis B (n = 10; 25.6%) and hepatitis C (n = 6; 15.4%). Of nine recipients who died, eight (88.8%) were co-infected with hepatitis A, two (22.2%) with hepatitis B and three (33.2%) with hepatitis C.

Table 1. Serological profiles of liver graft recipients in respect to IgM and IgG antibodies.

Characteristic	**Total (n = 48)**		**G1**		**G2**		**G3**	
Serological profile			IgG-/IgM-		IgG+/IgM-		IgG+/IgM+	
	n	%	n	%	n	%	n	%
Recipients	48	100.0	20	41.7	26	54.1	2	4.2

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Symptoms								
Fever	17	100.0	7	41.2	10	58.8	0	0.0
Pulmonary nodule	1	100.0	0	0.0	1	100.0	0	0.0
Headache	8	100.0	3	37.5	5	62.5	0	0.0
hepatosplenomegaly	23	100.0	9	39.1	14	60.9	0	0.0
Encephalopathy	10	100.0	4	40.0	6	60.0	0	0.0
Hepatitis								
A	39	100.0	16	41.0	22	56.4	1	2.6
B	15	100.0	5	33.3	9	60.0	1	6.7
C	9	100.0	3	33.3	6	66.7	0	0.0
Deaths								
Yes	20	41.7	9	45.0	9	34.6	2	100.0
No	28	58.3	11	55.0	17	65.4	0	0.0

*Some patients were co-infected with more than one type of hepatitis.

4. Discussion

The results of this study demonstrate that T. gondii infection of liver recipients, defined as the presence of IgM and/or IgG anti-T. gondii antibodies in their serological profile, is not associated with post-transplant symptoms such as fever, pulmonary nodules, headache, hepatosplenomegaly and encephalopathy. This lack of association is supported by the occurrence or not of post-transplant death. Co-infection was higher for hepatitis A compared to hepatitis B and C.

T. gondii infection is common in humans with its prevalence varying according to region with values being higher in countries with lower socioeconomic development [25,26]. In this context, organ recipients are not exempt from infection by this apicomplexan parasite as it can be acquired through transplantation [21,27]. In their review article, Galván-Ramirez et al. report that a large proportion of donors are infected and that T. gondii cysts present in the graft, when transmitted to recipients, can constitute a significant problem.

The serological investigation of T. gondii infection in organ recipients and donors is carried out using the same methods as those applied to other types of patients and blood donors. In cases reactive for IgM and/or IgG anti-T. gondii antibodies, chemoprophylaxis is used with the aim of minimizing the risks of cyst reactivation in the graft, especially in immunosuppressed individuals (Derouin & Pelloux, 2008). There are reports demonstrating that the reactivation of T. gondii infection delays between one week and nine months after the start of immunosuppression and that this condition may favor death in some recipients [28–32].

Transplantation is the first-line treatment for patients with liver failure; the quality of life is good and the one-year survival rate is around 85%. However, infections in the postoperative period are a significant cause of morbidity and mortality. There are reports that describe mortality rates of 26% in the postoperative period. In 88% of these cases, mortality is related to infections. Despite the importance of these data, the prevalence of infections prior to transplantation and their influence on morbidity and mortality in the post-transplant period are still scarce.

In a review published in 2018, Dhakal et al. reported that the high rate of morbidity in liver transplantation is related to toxoplasmosis. These authors argue that screening to identify T. gondii infection in liver recipients is low-cost and that its routine use would benefit this group of at-risk patients [33].

There are reports that the transmission rate of T. gondii from seropositive donors to seronegative recipients in liver transplantation is around 20% (Schaffner, 2001). This is lower than the figure reported for heart transplants (50-75%) but it is much higher than that observed in kidney transplants (1%). It is argued that the use of serological and molecular laboratory methods associated with chemoprophylaxis and follow-up can contribute to reducing transmission rates of T. gondii from donors to recipients. These strategies favor the early detection of infection as well as possible reactivation of tissue cysts in the grafts [34].

This study demonstrated that T. gondii infection is not associated with post-transplant signs and symptoms nor with the occurrence of death in liver transplantation. Its results draw attention to the need of further studies that might contribute to knowledge about possible reactivation of previous infections in recipients and the transmission of T. gondii through the graft in order to reduce the possible risk of death in recipients, specially in South America where T. gondii strain are more virulent.

The data reported by this study need to be interpreted with caution due to potential limitations such as the retrospective nature of the study as most information about the serological profile of donors and their respective recipients was not available for analysis. As a consequence, the patient sample was small and the analysis and interpretation of data is possibly unsound.

5. Conclusions

Data from this study demonstrate that the prevalence of T. gondii infection in liver recipients is high and, therefore, although there is no definitive proof from the results of this study screening for infection for this parasite should be intensified until further studies are carried out. Furthermore, co-infection with hepatitis A was substantial, especially in the patients who died in the post-transplant period.

Author Contributions: CCB is head of the FAMERP Toxoplasma Research Group; CCB and RCMA conceived and designed the study; FCBLP, GBP, RCMAS, RFS, FIMSJr selected the patients and developed the clinical diagnosis; GBP, CCB, NZ, FCBLP and LCM were responsible for the data analysis; GBP, RCMAS, NZ, FCBLP were responsible for the manuscript writing. All the authors approved the final version of the manuscript.

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Institutional Review Board Statement: Ethics statement of study. This retrospective study was approved by the Internal Review Board (IRB) of the Medical school of São José do Rio Preto (FAMERP) on 11/04/2019 under the protocol number CAAE 00726618.6.0000.5415. Because of the nature of the study, a signed consent form was waived.

Data Availability Statement: Following Brazilian Law for Transplantation no data will be shared.

Conflicts of Interest: The authors declare no conflict of interest.

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