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Hematological and Biochemical Analysis of Sheep Naturally Infected with *Toxoplasma Gondii* and *Neospora Caninum*

Análise Hematológica e Bioquímica de Ovinos Naturalmente Infectados por Toxoplasma Gondii e Neospora Caninum

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ABSTRACT

Introduction: *Toxoplasma gondii* and *Neospora caninum* are recognized as significant causes of reproductive issues in sheep; however, studies examining the impact of natural infections on clinical pathology parameters remain limited. **Objectives:** To determine whether natural infections by *Toxoplasma gondii* and *Neospora caninum* may influence hematological and biochemical parameters. **Methods:** Blood samples were collected from 119 sheep in Rio de Janeiro, Brazil, and divided into four groups based on the presence of IgG antibodies: *anti-T. gondii* and *anti-N. caninum*. The tests used were MAT and ELISA. **Results:** *T. gondii*-infected animals had significantly increased values for the MCV, MCHC, and the number of basophils compared to the seronegative group ($P<0.05$). The number of leukocytes, erythrocytes, lymphocytes, eosinophils, and segmented neutrophils was statistically lower in the infected group than in the uninfected group. On the other hand, there were no significant differences in the hematological and serum biochemical parameters between the *N. caninum*-infected and uninfected sheep. Increasing *T. gondii* antibody titers also did not interfere with any analyzed parameters ($P>0.05$). **Conclusion:** No significant changes were observed in the hematological and serum biochemical parameter values among sheep infected with *N. caninum*. Analyzing the hematological and serum biochemical parameters of sheep naturally infected with *Toxoplasma gondii* and *Neospora caninum* would not aid in diagnosing these diseases.

Descriptors: Hematology, Biochemical, Ruminants, Toxoplasmosis

RESUMO

Introdução: *Toxoplasma gondii* e *Neospora caninum* são causas conhecidas de problemas reprodutivos em ovelhas, mas os estudos sobre a influência da infecção natural nos parâmetros de patologia clínica são escassos. **Objetivos:** Determinar se a infecção natural por *T. gondii* e *N. caninum* podem interferir nos parâmetros hematológicos e bioquímicos de ovinos. **Métodos:** Amostras de sangue de 119 ovelhas foram coletadas no Rio de Janeiro, Brasil, e divididas em quatro grupos de acordo com a presença de anticorpos do tipo IgG: *anti-T. gondii* e *anti-N.* caninum; foram utilizados MAT e ELISA. **Resultados:** Os animais infectados com *T. gondii* apresentaram valores significativamente aumentados para o MCV, a MCHC e o número de basófilos em comparação com o grupo soronegativo ($P<0,05$). O número de leucócitos, eritrócitos, linfócitos, eosinófilos e neutrófilos segmentados foi estatisticamente menor no grupo infectado em comparação com o grupo não infectado. Por outro lado, não houve diferenças significativas nos parâmetros hematológicos e bioquímicos séricos entre as ovelhas infectadas e não infectadas por *N. caninum*. O aumento dos títulos de anticorpos contra *T. gondii* também não afetou nenhum parâmetro analisado ($P>0,05$). **Conclusão:** Nenhum valor dos parâmetros hematológicos e bioquímicos séricos foi significativamente alterado entre os ovinos infectados por *N. caninum*. A análise dos parâmetros hematológicos e bioquímicos séricos de ovinos naturalmente infectados por *T. gondii* e *N.caninum* não pareceu contribuir para o diagnóstico das doenças.

Descritores: Hematologia, Bioquímica, Ruminantes, Toxoplasmose

INTRODUCTION

Toxoplasma gondii is a widely distributed intracellular obligate parasite that infects animals and humans[1]. It has a similar structure to another coccidium called *Neospora caninum*, although they have distinct biological aspects[2-3]. Toxoplasmosis is a common cause of abortion in sheep and might lead to neonatal death, mummification, stillbirth, or the birth of debilitated lambs[1,3-4]. Therefore, *T. gondii* infection in sheep has a major economic impact on sheep farming[1,5-6], especially when related to reproductive disorders or reinfection in primiparous pregnant females[7]. Generally, among commercial farm animals, goats, sheep,

and pigs are more susceptible to infection by *T. gondii* compared to cattle, horses, and birds, which rarely show signs of infection[8]. The prevalence of *T. gondii* is higher in conventionally bred pigs, sheep, and poultry than in cattle and more frequently found in meat products from organic rather than conventionally bred meat animals[9].

Neosporosis in farm animals, including sheep, also causes economic losses due to reproductive disorders such as abortions and neonatal deaths, similar to toxoplasmosis[3,10]. Transmission can occur horizontally or vertically through a transplacental route, which might be exogenous or endogenous[11]. A meta-analysis review identified a prevalence of approximately 18% of *N. caninum* in sheep from Brazil, causing abortions and reproductive changes[12-13].

The objective of this study was to determine whether naturally acquired infections with *T. gondii* and *N. caninum* in sheep could influence changes in hematological and biochemical parameters, potentially aiding in the diagnosis of toxoplasmosis and neosporosis in this species. This consideration is based on their potential to cause reproductive changes and, consequently, economic losses.

METHODS

Ethical Approval

This study was approved by the Ethics Committee of Animal Use (CEUA) of Federal Fluminense University (UFF), license number 0011109.

Sample Collection and Grouping

Blood samples of 119 sheep were collected from farms in Rio de Janeiro State with a history of reproductive disorders. Animals were serologically tested for the presence of anti-*N. caninum* and anti-*T. gondii* antibodies and distributed into four groups, as it follows: 25 seropositive and 35 seronegative samples for anti-*T. gondii* antibodies and 13 seropositive and 46 seronegative samples for anti-*N. caninum* antibodies.

Detection of Antibodies

Detection of Anti-*N. caninum* Antibodies: For the detection of anti-*N. caninum* IgG type antibodies, we used an enzyme-linked immunosorbent assay (ELISA) for ruminants (CHEKIT Neospora, IDEXX Switzerland AG, Liebefeld-Bern, Switzerland) performed according to the manufacturer's instructions. The samples were analyzed using a microplate reader (Thermo Plate) at a 450 nm-wavelength.

Detection of Anti-*T. gondii* Antibodies: For the detection of anti-*T. gondii* IgG type antibodies; the samples were subjected to the Modified Agglutination Test (MAT) according to the protocol of Dubey and Desmonts (1987)[14]. All samples with agglutinating activity at a 1:25 dilution were considered positive[1]. These serum samples were subsequently titrated against reacting antigens using serial two-fold dilutions up to 1:3200.

Blood and Biochemical Tests

Complete blood counts were performed with the T-890 Automated Cell Counter (Coulter Corp, Hialeah, Florida, USA). The biochemical tests were performed with an automatic multi-channel unit (Bio 2000 Semi-Automated Analyzer) using commercial kits (Diagnostic Labtest SA, Brazil) according to the manufacturer's instructions. The following enzymes and proteins were tested: aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), creatinine phosphokinase (CK), total protein, and urea.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism 5.0. The normality of the data was verified using the Kolmogorov-Smirnov test. For the comparison of the two groups; the Mann-Whitney test was used for non-parametric data; the Student's t-test was used for parametric data. A P-value of <0.05 was considered statistically significant. Additionally, the influence of antibody titers was verified using the Mann-Whitney test to compare two titer groups: 25 to 100 and 200 to 3200.

RESULTS

Hematological Parameters

Animals infected with *Toxoplasma gondii* exhibited significantly increased mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and basophil counts compared to the seronegative group (P<0.05). Conversely, leukocyte, erythrocyte, lymphocyte, eosinophil, and segmented neutrophil counts were significantly lower in the infected group compared to the uninfected group (Table 1).

Table 1. Mean hematological values of seronegative and seropositive sheep for the presence of anti-*Toxoplasma gondii* antibodies.

Parameter	Units	Reference values[25]	Anti-Toxoplasma gondii antibodies				P value
			n	Negative	n	Positive	
Erythrocytes	nx106/µl	9-15	35	11.00± 1.67	25	9.10± 2.08	0.0003
Haematocrit	%	27-45	35	30.69± 6.56	25	29.20± 5.82	0.0984
MCV	Fl	28-40	35	30.11 ± 2.71	25	32.51 ± 2.08	0.0015
MCHC	%	31-34	35	32.11 ± 1.64	25	35.48 ± 2.90	0.0001
Leukocytes	mean/ml	4000-12000	35	10544 ± 4321	25	7664 ± 3284	0.0057
Haemoglobin	g/dl	9-15	35	10.50 ± 1.27	25	10.28 ± 1.80	0.7020
Basophils	% 103xmm³	0-3 0-300	35	0 ± 0 0 ± 0	25	0.36 ± 1.22 28 ± 40	0.0152
Neutrophils Segmented	% 103xmm³	10-50 1500-9000	35	42.60 ± 13,10 4491 ± 566	25	56.96 ± 16.97 4365 ± 557	0.0430
Lymphocytes	% 103xmm³	40-75 2000-9000	35	48.80 ± 13.98 5145 ± 604	25	37.68 ± 16.05 2888 ± 527	0.0088
Monocytes	% 103xmm³	0-6 0-600	35	2.51 ± 1.91 265 ± 82	25	2.12 ± 2.13 162 ± 70	0.2560
Eosinophils	% 103xmm³	0-10 0-1000	35	5.88 ± 5.90 620 ± 255	25	2.80 ± 5.06 214 ± 166	0.0023

In contrast, there were no significant differences (P>0.05) in haematological parameters between the *Neospora caninum*-infected and uninfected sheep (Table 2).

No significant associations were found between *T. gondii* antibody titers and hematological parameters (P>0.05). Although basophil counts were initially considered significant in the 200 to 3200 titer group; this result was deemed unreliable due to an abnormally high count in a single animal.

Biochemical Parameters

The results of biochemical tests for anti-*T. gondii* seronegative and seropositive animals are presented in Table 3. There were no significant differences (P>0.05) in aspartate aminotransferase (AST), albumin, creatinine, and gamma-glutamyl transferase (GGT) levels between the groups. However, alanine aminotransferase (ALT), urea, total protein, and creatine kinase (CK) levels differed significantly between seronegative and seropositive groups (P<0.05). Specifically, ALT levels were lower in seropositive animals compared to seronegative ones, while urea, CK, and total protein levels were higher. When compared to the reference values for the species, urea and total protein remained within normal ranges, ALT was elevated in the uninfected group, and CK was elevated in both groups.

Similarly, the values for AST, ALT, urea, total protein, GGT, creatinine, CK, and alkaline phosphatase (ALP) did not differ significantly between anti-*N. caninum* seropositive and seronegative animals (P>0.05). However, albumin levels were significantly higher in the infected animals compared to the seronegative ones (P<0.05), with the infected group showing slightly increased values compared to the species' reference range (Table 4).

Table 2. Mean haematological values of seronegative and seropositive sheep for the presence of anti-*Neospora* caninum antibodies.

Parameter	Units	Reference values[14]	Anti-Neospora caninum antibodies				P Value
			n	Negative	n	Positive	
Erythrocytes	nx10^6/µl	9-15	46	10.00 ± 2.14	13	10.80 ± 1.7	0.1701
Haematocrit	%	27-45	46	29.38 ± 6.59	13	32.45 ± 4.6	0.2373
MCV	Fl	28-40	46	31.42 ± 2.66	13	30.34 ± 2.70	0.1694
MCHC	%	31-34	46	33.38 ± 2.18	13	33.88 ± 4.46	0.8549
Leukocytes	mean/ml	4000-12000	46	9421 ± 4507	13	9446 ± 2521	0.5958
Haemoglobin	g/dL	9-15	46	10.30 ± 1.62	13	10.78 ± 1.03	0.6277
Basophils	% 10^{3}xmm^3	0-3 0-300	46	0.19 ± 0.90 18 ± 41	13	0 ± 0 0 ± 0	0.2751
Neutrophils Segmented	% 10^{3}xmm^3	10-50 1500-9000	46	48.49 ± 18.07 4569 ± 1546	13	48.61 ± 11.90 4592 ± 300	0.9053
Lymphocytes	% 10^{3}xmm^3	40-75 2000-9000	46	44.70 ± 16.61 4267 ± 752	13	43.00 ± 13.23 4062 ± 334	0.7008
Monocytes	% 10^{3}xmm^3	0-6 0-600	46	2.05 ± 1.77 199 ± 78	13	2.77 ± 2.28 262 ± 57	0.3115
Eosinophils	% 10^{3}xmm^3	0-10 0-1000	46	3.67 ± 5.11 345 ± 230	13	5.38 ± 6.26 508 ± 158	0.1767

Table 3. Mean serum biochemical values of seropositive and seronegative sheep for the presence of anti-*Toxoplasma gondii* antibodies.

Parameter	Units	Reference values[25]	Anti-Toxoplasma gondii antibodies				P value
			n	Negative	n	Positive	
ALT	U/L	30±4	25	31.84 ± 8.42	25	24.88 ± 8.75	0.0090
AST	U/L	60-280	25	124.64 ± 30.24	25	131.08 ± 41.35	0.6975
Creatinine	g/dL	1.2-1.9	25	0.78 ± 0.11	25	0.81 ± 0.21	0.9147
Urea	mg/dL	2.86-7.14	25	3.06 ± 1.41	25	4.12 ± 1.32	0.0039
TP	g/dL	6-7.9	25	6.39 ± 1.36	25	7.10 ± 1.27	0.0140
Albumin	g/dL	2.4-3	25	3.19 ± 0.61	25	2.80 ± 0.92	0.0912
GGT	U/L	20-52	24	44.25 ± 14.06	24	47.68 ± 29.00	0.9013
CK	mg/dL	8.1-12.9	24	24.00 ± 18.00	24	44.40 ± 20.50	0.0001

Table 4. Mean serum biochemical values for seropositive and seronegative sheep for the presence of anti-*Neospora caninum* antibodies.

Parameter	Units	Reference values[25]	Anti-Neospora caninum antibodies				P value
			n	Negative	n	positive	
ALT	U/L	30±4	36	27.59 ± 9.26	13	29.54 ± 8.86	0.5030
AST	U/L	60-280	36	130.08 ± 39.59	13	123.92 ± 24.88	0.7681
Creatinine	mg/dL	1.2-1.9	36	0.82 ± 0.17	13	0.75 ± 0.15	0.3061
Urea	mg/dL	2.86-7.14	36	3.70 ± 1.43	13	3.11 ± 1.39	0.1566
TP	g/dL	6-7.9	36	6.92 ± 1.37	13	6.20 ± 1.23	0.0912
Albumin	g/dL	2.4-3	36	2.84 ± 0.75	13	3.37 ± 0.84	0.0264
GGT	U/L	20-52	35	46.03 ± 19.25	11	39.54 ± 11.07	0.2400
CK	mg/dL	8.1-12.9	32	38.40 ± 24.10	13	23.30 ± 8.00	0.1257
ALP	U/L	68-387	16	189.75 ± 130.35	11	220.45 ± 105.57	0.4152

No significant associations were found between *T. gondii* antibody titers and biochemical parameters (P>0.05).

DISCUSSION

Haematological and biochemical analyses of sheep naturally infected by *Toxoplasma gondii* and *Neospora caninum* are scarce. Establishing haematological and biochemical parameters for these infections is crucial, as they can indicate a chronic infection in sheep, a species in which preventing reproductive losses are economically important. The pathogenicity of toxoplasmosis varies according to the dose and strain of the parasite. In South America, particularly in Brazil, atypical strains predominate and are considered virulent[1]. Hence, we focused on naturally infected animals in this particular experiment.

In this study, hematological parameter variations were detected in sheep naturally infected with *T. gondii*, but not in those infected with *N. caninum*. *T. gondii* seropositive and seronegative sheep did not differ in their hematocrit, hemoglobin, and monocyte counts, and all these values were within the reference values for the species[14]. This consistency aligns with findings by Oliveira *et al.* (2001)[15] in cattle and Tiwari *et al.* (1982)[16] in humans. However, *T. gondii*-infected animals had significantly increased MCV, MCHC, and basophil counts compared to the seronegative group. Leukocyte, erythrocyte, lymphocyte, eosinophil, and segmented neutrophil counts were statistically lower in the infected group. These findings have suggested that *T. gondii* infection influences these specific hematological parameters, although they remained within the species' reference values[14].

In pigs experimentally infected with the *T. gondii* ME-49 strain, a significant increase in neutrophils was observed seven days post-infection, indicating an immune response[17]. Conversely, a tendency for neutropenia was observed in *T. gondii*-infected pigs[18] and naturally infected cats[19]. Lymphopenia was also reported in dogs infected with distinct pathogenic strains of *T. gondii*[20]. Lashari *et al.* (2020)[21] reported significant changes in hematological parameters such as hemoglobin, total leukocytes, lymphocytes, platelets, and erythrocytes in small ruminants like sheep infected by *T. gondii*.

Regarding biochemical tests, normal values for AST, albumin, GGT, urea, and proteins[22] were observed in *T. gondii*-infected sheep. Similarly, Abreu *et al.* (2001)[20] have observed no change in urea levels in dogs experimentally infected with *T. gondii*. AST was also within the normal range in humans with toxoplasmosis[16]. However, creatinine, ALT, and CK values were altered in the *T. gondii* seropositive and seronegative groups based on reference values for sheep[22]. Despite lower creatinine values, there were no differences between seropositive and seronegative groups, indicating this change cannot be attributed to an abnormality. Decreased creatinine levels have been reported in a marsupial (*Macropus rufogriseus*) in Germany, with the seropositive animal presenting clinical signs typical of acute infection[23]. The animals in this study are more likely chronically infected as specific IgG antibodies were detected in their blood without clinical signs; however, IgM antibodies were not analyzed.

Analysis of CK enzyme values revealed significant differences between *T. gondii* seropositive and seronegative sheep, with both groups presenting values above the normal reference range for sheep[22]. Serum creatine kinase activity increases in cases of muscle necrosis in dogs infected with *T. gondii*[3]. Significant changes in ALT values were identified in the *T. gondii* seropositive group, with values lower than the reference range for sheep[22]. A significant decrease in ALT values was also observed in rabbits 11 days post-infection with *T. gondii* tachyzoites[24], indicating potential liver compromise[25]. Conversely, serum ALT showed an increasing trend 6 days post-infection in pig groups infected with *T. gondii*, likely due to direct hepatic injury from parasitic replication[17]. Marked increases in ALT and AST have been noted in animals with acute hepatic and muscle necrosis[1].

According to Dubey (2022)[1], MAT titers of 1:100 or above indicate persistently infected sheep, suggesting a high burden of tissue cysts. Therefore, we also compared hematological and biochemical parameters between animal groups with low and high antibody levels. No associations were detected, indicating these parameters cannot detect massive infections in sheep.

The results of hematological and biochemical analyses in *N. caninum* seropositive and seronegative sheep did not support their use as additional diagnostic tools. This aligns with a study by Pivatto *et al.* (2023)[12], which found no hematological changes in experimentally infected *N. caninum* sheep, consistent with the present study where values remained within the reference range for the species[14]. These findings support the hypothesis that bradyzoites in chronically infected animals do not cause an inflammatory response leading to hematological changes[26]. Similar results were reported for cows and dogs infected with *N. caninum*[27-28]. In dogs, differential leukocyte counts included lymphocytes, monocytes, macrophages, neutrophils, and eosinophils in decreasing numbers[3].

Biochemical values for AST, ALT, urea, protein, GGT, and alkaline phosphatase did not differ between *N. caninum* seropositive and seronegative sheep and were within the normal range for the species[22]. These outcomes are consistent with Knowler *et al.* (1995)[27], who reported normal biochemical values in an *N. caninum* seropositive dog. However, serum ALT can increase in dogs with hepatic inflammation[3].

Conversely, biochemical values for CK, creatinine, and albumin were altered in *N. caninum* seropositive and seronegative groups based on reference values for sheep. CK values were increased in *N. caninum* seropositive sheep but also elevated in seronegative animals compared to normal reference values for sheep[22]. Increased CK levels have been observed in dogs with muscle disease[3] and in dogs naturally infected with *N. caninum*[29]. Ruehlmann *et al.* (1995)[30] associated increased CK values with polymyositis caused by *N. caninum* infection, attributing the increase to myositis or neurological paralysis from parasitism[28]. However, these dogs had acute infections, unlike the chronically infected animals in this study.

Mean creatinine values did not differ between *N. caninum* seropositive and seronegative sheep. Therefore, the observed decrease cannot be attributed to *N. caninum* infection as it was observed in both groups[22]. Albumin values were significantly increased in infected animals compared to seronegative ones, but they were only slightly above the normal range for sheep[22], indicating this parameter is not a reliable additional test for *N. caninum* diagnosis.

CONCLUSION

The analysis of hematological and serum biochemical parameters in sheep naturally infected by *Toxoplasma gondii* and *Neospora caninum* does not contribute to the diagnosis of these diseases. Further studies focusing on IgM-positive animals are necessary to determine if there is any specific correlation between these parameters and acute infections for both parasites.

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