

## THROMBOCYTOPENIA AND LEPTOSPIROSIS

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### SUMMARY

The present study has intended to contribute to the elucidation of the pathogenic mechanisms, involved in the thrombocytopenia and in the bleeding diathesis seen in the course of **Leptospirosis**. The group of cases included in the present prospective study consisted of 30 patients with **Leptospirosis**, admitted to the Infectious and Parasitic Diseases Ward, Hospital das Clínicas, Faculty of Medicine, University of São Paulo. The following possible mechanisms of thrombocytopenia have been considered and therefore investigated: platelet consumption, due to disseminated intravascular coagulation; immune-mediated platelet destruction, due to platelet-associated antibodies and an inhibited platelet production in the bone marrow. Thrombocytopenia occurred in 86.6% of 30 patients and did not seem to be immune-mediated by platelet-associated antibodies. Furthermore it did not seem to be due to a disseminated intravascular coagulation consumption. Although there was a statistically-significant correlation between bone marrow platelet production and platelet counts we think that the static microscopic examination of a bone marrow aspirate cannot accurately depict the dynamic mechanisms of platelet production when these cells are being consumed in peripheral blood. Vasculitis should be considered as the most important factor for the pathogenesis of the bleeding disturbances in **Leptospirosis**. However, we believe that thrombocytopenia, uremia and coagulation disorders, individually or as a group, should be included among the contributing factors that lead to and worsen bleeding episodes, which represent the leading cause of death in this disease.

**KEY WORDS:** Leptospirosis; thrombocytopenia; hemorrhagic diathesis.

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### INTRODUCTION

Thrombocytopenia has frequently been associated with **Leptospirosis** and, although its occurrence varies considerably (BERMAN et al., 1973<sup>3</sup>; EDWARDS et al., 1982<sup>11</sup>; EDWARDS et al., 1986<sup>12</sup>; HEATH Jr. et al., 1965<sup>18</sup>; RAOULT et al., 1983<sup>26</sup>) (in some regions of the world it is very prevalent), it is not yet fully understood.

The object of this paper is to contribute to the study of thrombocytopenia occurring in **Leptospirosis** based on an evaluation of the role of antibody against platelets, medular inhibition of their production, and the possibility of their consumption through disseminated intravascular coagulation.

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## PATIENTS AND METHODS

This prospective study was designed to include 30 consecutive patients admitted to the Infectious and Parasitic Diseases Ward, Hospital das Clínicas, Faculty of Medicine, University of São Paulo, due to severe forms of **Leptospirosis**.

The diagnosis of **Leptospirosis** was based on the criteria adopted by the "United States Department of Health, Education and Welfare" (FEIGIN & ANDERSON, 1975)<sup>13</sup>.

The patients were selected without taking into consideration their initial blood platelet count or any other specific clinical or laboratory manifestations.

The following laboratory tests were performed:

1. Blood platelet count — reference range: 150.000 to 450.000/mm<sup>3</sup> (BRECHER & CRONKITE, 1950)<sup>6</sup>.

The first count was performed within 24 to 48 hours of hospitalization and repeated regularly during the follow-up.

Since the limits adopted by different authors vary, it worths special mention that in the present paper, thrombocytopenia was defined as a platelet count under 150.000/mm<sup>3</sup>.

2. Coagulation study comprising the following tests:

- a) Prothrombin time (QUICK, 1942)<sup>24</sup>
- b) Recalcination time (QUICK, 1942)<sup>24</sup>
- c) Thrombin time (BONSNES & SWEENEY, 1955)<sup>5</sup>
- d) Activated partial thromboplastin time (DENSON, 1976)<sup>9</sup>
- e) Fibrinogen (SCHULZ, 1955)<sup>27</sup>
- f) Factor V (DOUGLAS, 1976)<sup>10</sup>
- g) Factor VIII (De ANGULO & FROMMEL, 1974)<sup>7</sup>
- h) Fibrin degradation products (MERSKEY et al., 1969)<sup>22</sup>
- i) Anti-thrombin III (BIGGS et al., 1970)<sup>4</sup>.

3. Anti-platelet antibodies — at the beginning of this study complement fixation was

used. Later on direct and indirect immunofluorescence methods were added.

4. Bone marrow aspirate — performed at hospitalization. The results were descriptive.

5. Microagglutination tests with live leptospire performed at Instituto Adolfo Lutz, São Paulo.

6. The following tests were also made:

- a) Serum urea — reference range: 10 to 45 mg/100 ml;
- b) Serum creatinine — reference range: 0.6 to 1.4 mg/100 ml;
- c) Serum bilirubin — reference range: direct — 0 to 0.4 mg/100 ml; indirect — 0.1 to 0.6 mg/100 ml; total — 0.2 to 1.0 mg/100 ml;
- d) Serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyltransferase, lactate dehydrogenase;
- e) Complete blood count.

7. Acute renal failure definition included serum creatinine levels above 1.4 mg/100 ml in at least 3 different instances during the follow-up.

## RESULTS

Twenty-two patients (75.8%) were admitted to Hospital during the first week of illness.

**L. icterohaemorrhagiae** was the most frequent serotype (12 cases).

Twenty-eight patients (93.3%) presented elevated urea levels at hospitalization, with values from 31 to 429 mg/100 ml (mean: 143.9 ± 94.3).

Twenty-six patients (86.6%) presented elevated creatinine values at hospitalization, with values from 0.9 to 14.0 mg/100 ml (mean: 3.94 ± 2.51).

Acute renal failure occurred in 26 patients (86.6%). In 29 cases (96.6%) jaundice was presented at hospitalization, and in only 2 cases it was predominantly due to indirect bilirubin (6.8%). Total bilirubin values varied from 0.6 to 50.7 mg/100 ml.

The mean platelet count was significantly lower in the group of the 15 patients with the highest serum urea levels than the other group of 15 patients.

$$T_{22} = 1.818 > T_{22:0.05} = 1.717$$

TABLE  
Serum urea levels and blood platelet counts on admission

Patient	Serum urea level (mg/100 ml)	Platelet count (/mm <sup>3</sup> )
1	60	50.000
2	31	40.000
3	200	10.000
4	84	45.000
5	84	15.000
6	26	155.000
7	218	165.000
8	180	30.000
9	84	80.000
10	80	125.000*
11	182	35.000
12	194	9.000
13	132	95.000
14	120	65.000
15	109	20.000
16	42	240.000
17	169	40.000
18	248	31.000
19	141	60.000
20	110	40.000
21	93	280.000
22	83	70.000
23	75	100.000
24	177	16.000
25	202	25.000
26	95	60.000
27	429	63.000
28	112	39.000
29	147	80.000
30	409	5.000

\* — Patient number 10 was the only thrombocytopenic with more than 100.000 platelets/mm<sup>3</sup>.

However the difference in mean platelet count was not significant between the groups of 15 patients with the highest and lowest creatinine levels.

$$T_{23} = 1.121 < T_{23:0.05} = 1.714$$

The mean serum urea level in the group of 16 patients who presented hemorrhages was 170.3 ± 112.7 mg/100 ml (range: 31 to 429 mg/100 ml), significantly higher than the mean value among the 14 patients who did not have hemorrhages: 113.6 ± 57.9 mg/100 ml (range: 26.0 to 218.0 mg/100 ml). P (t > 1.764) = 0.0452.

The mean serum creatinine level in the group of 16 patients who presented hemorrhages was 4.59 ± 2.97 mg/100 ml (range: 1.0 to 14.0 mg/100 ml) and was not considered significantly different from the mean value obtained among the other 14 patients: 3.62 ± 2.25 mg/100 ml (range: 0.6 to 6.8 mg/100 ml). P (t > 1.019) = 0.1584.

Eleven patients underwent dialysis and their mean platelet count was 41.091 ± 27.402 (range: 5.000 to 95.000/mm<sup>3</sup>) — significantly lower than the mean value obtained among non-dialysed patients: 86,105 ± 75,897 (range: 15,000 to 280,000/mm<sup>3</sup>). P (t > 2.336) = 0.0139.

Two patients underwent hemodialysis soon after hospital admission and were excluded from the coagulation study for having used heparin.

Among the 28 cases studied an elevation of the prothrombin time was noted in 3 cases (10.7%) and an elevation of the activated partial thromboplastin time in 8 (28.5%). In 18 patients the level of fibrinogen was measured and it was found elevated in 8 cases (44.4%).

Antibodies against platelets were found in 3 patients, and in only one of these both the complement fixation and the indirect immunofluorescence tests were positive. In all the cases the direct immunofluorescence test was negative.

The results of the bone marrow aspirates were the following: in 24 patients the number of megakaryocytes was normal but in 13 of them the platelet production was low and all these 13 patients presented low blood platelet counts. In the remaining 11 patients the platelet production was normal but 7 of these had low blood platelet counts.

Five cases showed a low number of megakaryocytes; 3 of these cases presented a low platelet production and a low blood platelet count. The other 2 had a normal platelet production but a low blood platelet count. In only one patient the number of megakaryocytes in the aspirate was higher than normal; however the production of platelets was low, as well as the blood count. No significant relation was found between the number of megakaryocytes in the bone marrow aspirate and the blood platelet count.

$$P (X^2_c > 1.244) = 0.5369$$

A direct relation was found between the level of medular platelet production and the blood platelet count.

$$P = 0.0261$$

A low blood platelet count occurred in 26 (86.6%) of the 30 patients. Their mean initial count was 30,649/mm<sup>3</sup> (range: 5,000 to 125,000/mm<sup>3</sup>). In 4 cases (13.3%) the platelet count was normal. In 4 cases the platelet count was low until the moment of death which occurred on the: first, second, sixth and 13<sup>th</sup> day of hospitalization respectively. Nineteen of the 22 remaining cases had a normal count by the 7<sup>th</sup> day of hospitalization.

Sixteen (61.5%) of the 26 patients with initial low blood platelet counts had hemorrhages and their mean initial count was 43,312 ± 24,475/mm<sup>3</sup> (range: 5,000 to 95,000/mm<sup>3</sup>). The other 10 patients had a mean initial platelet count of 55,500/mm<sup>3</sup> ± 38,851/mm<sup>3</sup> (range: 9,000 to 125,000/mm<sup>3</sup>).

None of the 4 patients with an initially normal blood platelet count presented hemorrhages.

The mean time until normalization of the platelet count among the thrombocytopenic patients who had hemorrhages was 7 days, similar to the mean time among those without hemorrhages which was 5 days.

$$t_{16} = 1.057 < t_{16;0.05} = 1.746$$

There was no significant difference between the mean platelet count in the groups with or without hemorrhages.

$$P (t > 0.888) = 0.1917$$

Most frequent hemorrhagic manifestations were presented in skin (8), lower respiratory tract (6), upper respiratory tract (6) and digestive tract (5).

## DISCUSSION

The occurrence of hemorrhage in this study was related to higher serum levels of urea, sug-

gesting that uremia is a contributing factor to hemorrhage in **Leptospirosis**.

The mean platelet count in the dialysed patients was significantly lower than that among non-dialysed patients. It is important to note that 9 of the 11 patients who underwent dialysis presented hemorrhages — severe in 7 cases — and that all the 4 patients who died had undergone dialysis.

Our results of the coagulation study are similar to those obtained by others authors. GESZTI et al. (1957)<sup>15</sup> noted an elevation of prothrombin time in experimental **Leptospirosis**. In human **Leptospirosis**, RAMOS-MORALES et al. (1959)<sup>25</sup> and JAROONVESAMA et al. (1975)<sup>21</sup> noted hipoprothrombinemia in some cases. JAROONVESAMA et al. (1975)<sup>21</sup> and SITPRIJA et al. (1980)<sup>28</sup> found altered activated partial thromboplastin times.

High levels of fibrinogen had been described in **Leptospirosis** by SITPRIJA et al. (1980)<sup>28</sup> who attributed this phenomenon to the tissue lesion and to the vascular endothelial lesion caused by the leptospire. This explanation seems to us more acceptable than that given by HIGGINS & COUSINEAU (1977)<sup>20</sup> who, based on experimental work, interpreted this fibrinogen elevation as a compensatory over-production by the liver in response to a high consumption.

We did not find an elevation of fibrin degradation products (F.D.P.) different from SITPRIJA et al. (1980)<sup>28</sup> and EDWARDS et al. (1986)<sup>12</sup>. The former authors attributed this elevation to disseminated intravascular coagulation. EDWARDS et al. (1986)<sup>12</sup> however interpreted the F.D.P. elevation to a low hepatic clearance of these substances by the Kupffer cells, based on work by GANS & LOWMAN (1967)<sup>14</sup> who demonstrated the great importance of the mononuclear phagocytes in eliminating fibrin and its metabolites.

All these alterations in the blood coagulation are not specific and are neither related to disseminated intravascular coagulation nor directly related to the occurrence of hemorrhages in human **Leptospirosis**. They are due mainly to the hepatic dysfunction that occurs in this disease and to cholestasis leading to a lower vitamin K absorption.

There are technical difficulties in the study of antibodies against platelets. Complement fixation is a reasonably specific test (HARRINGTON, 1987)<sup>17</sup> and immunofluorescence appears to be quite a sensitive test (HARMON & MILLER, 1981)<sup>16</sup>, (HELMERHORST et al., 1980)<sup>19</sup>. Direct immunofluorescence was negative in all cases and is known to be more specific than the indirect reaction that can present false positive results due to the interference of serum factors on the platelet surface. This possibility must be considered, since HARRINGTON (1987)<sup>17</sup> demonstrated proteins in great quantity on the platelet surface whose removal created great difficulties.

Based on our results we believe the low blood platelet counts in **Leptospirosis** are not due to antiplatelet antibodies.

Our results of the bone marrow aspirates showed that all the 17 patients with low marrow platelet production presented a low blood platelet count.

However, 9 of the 13 patients with a normal marrow production also had a low blood platelet count.

There was no direct correlation between the number of megakariocytes and the blood platelet count, but there was a direct correlation between the bone marrow platelet production and blood platelet count.

We believe that it is very difficult to have a good idea of the dynamic mechanisms that lead to medular platelet production in the presence of "platelet consumption", through a random test of the bone marrow.

Thrombocytopenia was present in 26 (86.6%) of our patients. This allows us to consider thrombocytopenia a frequent occurrence among the severe forms of **Leptospirosis** in our environment. Of these 26 patients, 16 presented hemorrhages (61.5%) and were the only patients in our study to have bleeding episodes.

The blood platelet count was not significantly different between the group that had hemorrhages and that without hemorrhages. There was no significant difference in the duration of

thrombocytopenia when comparing these two groups.

The analysis of the data obtained in the present study, have led to the following statements and conclusions:

1) Thrombocytopenia is often seen in the course of severe **Leptospirosis** cases among us (86.6%).

2) Thrombocytopenia in patients with **Leptospirosis** does not seem to be immune-mediated, by platelet-associated antibodies.

3) The analysis of the obtained data has demonstrated no clinical or laboratory evidence of disseminated intravascular coagulation.

4) A statistically-significant correlation was noticed between bone marrow platelet production and platelet counts ( $p = 0.0261$ ). A possible inhibition of bone marrow platelet production, related to bacterial products (toxin) could not be ruled out. We think that the static examination of a bone marrow aspirate alone cannot accurately depict the dynamic mechanisms of platelet production when these cells are being consumed in peripheral blood.

5) Although thrombocytopenia may play a supporting role in the hemorrhagic syndrome in **Leptospirosis**, platelet counts in patients with or without hemorrhages, showed no statistically significant difference.

6) In the vast majority of cases (86.3%) platelet counts returned to normal values within 7 days after hospital admission.

7) There was no statistically significant difference in the mean time required for platelet counts to return to normal values, when patients with or without hemorrhages were compared.

8) The mean platelet count was significantly lower in patients with higher serum urea levels.

9) The mean serum urea level in patients with hemorrhages was significantly higher when compared to patients without hemorrhages, pointing out that uremia might contribute to

## the severity of bleeding disturbances in **Leptospirosis**

Vasculitis should be considered as the most important factor for the pathogenesis of the bleeding disturbances in **Leptospirosis**<sup>1, 2, 8, 23</sup>.

However, we believe that thrombocytopenia, uremia and coagulation disorders, each one separately or all together, should be included among the contributing factors that lead to and worsen bleeding episodes, which represent the leading cause of death in this disease.

### RESUMO

#### Trombocitopenia e Leptospirose

O propósito do presente trabalho é colaborar para o estudo da patogenia da plaquetopenia que ocorre na **Leptospirose**.

A pesquisa foi feita de maneira prospectiva e o grupo de casos foi constituído por 30 pacientes internados com hipótese diagnóstica de **Leptospirose** na Clínica de Doenças Infecciosas e Parasitárias do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo.

Investigou-se a possibilidade de haver consumo de plaquetas por coagulação intravascular disseminada, ou a possibilidade de destruição periférica de plaquetas por anticorpos e, se poderia haver inibição da produção de plaquetas em nível medular.

Para a investigação desejada foram utilizados os seguintes exames: contagem de plaquetas, tempo de protrombina, tempo de recalcificação, tempo de trombina, tempo de trombo-plastia parcial ativada, dosagem do fibrinogênio, dosagem do fator V, dosagem do fator VIII, dosagem dos produtos de degradação da fibrina, dosagem da antitrombina III, mielograma e pesquisa de anticorpos antiplaquetas. Foram ainda estudados o hemograma, a dosagem de uréia, a dosagem de creatinina, a dosagem das enzimas hepáticas (aspartatoaminotransferase, alaninaaminotransferase, desidrogenase láctica, gama-glutamiltanspeptidase e fosfatase alcalina), e a dosagem das bilirrubinas.

A análise dos dados obtidos no presente trabalho permitiu-se chegar às seguintes constatações e conclusões:

1ª) A plaquetopenia é freqüentemente encontrada na forma grave de **Leptospirose** ocorrida em nosso meio (86,6%).

2ª) A plaquetopenia da **Leptospirose** não parece ser mediada por anticorpos antiplaquetas.

3ª) A avaliação dos dados obtidos não mostrou haver evidências clínicas e laboratoriais de ocorrência de coagulação intravascular disseminada.

4ª) Verificou-se existência da relação de dependência entre a plaquetogênese medular e a contagem de plaquetas no sangue periférico ( $P = 0,0261$ ). A possibilidade de haver inibição da plaquetogênese medular por algum produto bacteriano (toxina) não pode ser totalmente afastada, porém acreditamos que o exame estático da medula óssea não pode dar-nos uma idéia precisa do mecanismo dinâmico da formação de plaquetas na presença de "consumo periférico".

5ª) Embora a plaquetopenia possa representar um fator contribuinte para a síndrome hemorrágica, não chegamos a uma diferença estatisticamente significativa entre a contagem das plaquetas nos pacientes plaquetopênicos que sangraram e nos que não apresentaram sangramento.

6ª) Na maioria dos casos (86,3%) a normalização da contagem das plaquetas ocorreu no período de sete dias após a internação.

7ª) Não houve diferença significativa entre as médias dos tempos de normalização da contagem de plaquetas nos pacientes que apresentaram e nos que não apresentaram sangramento.

8ª) Houve diferença significativa, entre as médias das contagens das plaquetas nos pacientes de níveis séricos menores e os níveis séricos mais elevados de uréia, sendo maior no primeiro grupo ( $t_{22} = 1,818 > t_{22;0.05} = 1,717$ ).

9ª) A média do nível sérico dos pacientes que apresentaram sangramento foi maior do que a

média do nível sérico de uréia dos pacientes que não sangraram, podendo-se afirmar que a uremia contribui para agravar o quadro hemorrágico na **Leptospirose**.

A vasculite deve ser considerada como fator mais importante na patogênese dos distúrbios hemorrágicos da **Leptospirose**<sup>1, 2, 8, 23</sup>, porém, acreditamos que a trombocitopenia, a uremia e os distúrbios da coagulação, isoladamente ou em conjunto, devem ser incluídos entre os fatores que agravam o quadro hemorrágico o qual representa hoje a principal causa de óbito na doença.

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