

Aminotransferases analysis in patients with dengue serotype IV

Análise das aminotransferases em pacientes com dengue sorotipo IV

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ABSTRACT

OBJECTIVE: To evaluate the aminotransferase levels in patients with dengue serotype IV. **METHODS:** We conducted a cross-sectional analysis of 3,596 people with laboratory-confirmed dengue. **RESULTS:** The analysis showed that 49.2% (1,768) had normal aminotransferase levels, 43.4% (1,559) had changes in levels by up to three times the upper limit of normal, 7.0% (253) had elevations three times the reference value and 0.4% (16) developed acute hepatitis. Patients with thrombocytopenia and hemoconcentration had major changes in the levels of enzymes ($p < 0.05$). Women were more susceptible to those changes than men ($p < 0.05$). The average AST and ALT were higher in dengue hemorrhagic type (147.51 ± 137.74 U/L and 111.54 ± 81.27 U/L) as compared to dengue fever (55.18 ± 52.06 U/L and 60.39 ± 57.50 U/L) ($p < 0.05$). Leukopenic patients had aminotransferases average lower compared to individuals without any drop in overall white blood cell count ($p < 0.05$). A total of 224 patients were submitted to hospitalization, with the AST average of 88.18 ± 100.47 U/L and ALT 77.95 ± 88.38 U/L, which is higher than the average in ambulatory patients ($p < 0.05$). **CONCLUSION:** A significant number of patients was found with altered levels of enzymes, which requires clinical laboratory monitoring for an extended period.

Keywords: Dengue; Transaminases; Liver/injuries

RESUMO

OBJETIVO: Avaliar os níveis de aminotransferases em pacientes com dengue sorotipo IV. **MÉTODOS:** Foi realizada uma análise transversal de 3.596 pessoas com dengue confirmada laboratorialmente. **RESULTADOS:** A análise mostrou que 49,2% (1.768) tinham níveis normais de aminotransferases, 43,4% (1.559) mostraram alterações nos níveis em até três vezes o limite superior da normalidade, 7,0% (253) apresentaram elevações três vezes o valor de referência e 0,4% (16) desenvolveram hepatite aguda. Os doentes com trombocitopenia e hemoconcentração tiveram grandes alterações nos níveis enzimáticos ($p < 0,05$). As mulheres foram mais suscetíveis a essas alterações do que os homens ($p < 0,05$). As médias de AST e ALT foram maiores na dengue do tipo hemorrágica ($147,51 \pm 137,74$ U/L e $111,54 \pm 81,27$ U/L) em comparação com dengue clássica ($55,18 \pm 52,06$ U/L e $60,39 \pm 57,50$ U/L) ($p < 0,05$). Pacientes leucopênicos tiveram a média de aminotransferases menor em comparação com os indivíduos sem qualquer queda na contagem global de glóbulos brancos ($p < 0,05$). Um total de 224 pacientes foi submetido a hospitalização, com a média de AST $88,18 \pm 100,47$ U/L e ALT $77,95 \pm 88,38$ U/L, o que é mais elevado do que a média em doentes ambulatoriais ($p < 0,05$). **CONCLUSÃO:** Um número significativo de pacientes foi identificado com níveis alterados de enzimas, o que exige acompanhamento clínico e laboratorial por um período prolongado.

Descritores: Dengue; Transaminases; Fígado/lesões

INTRODUCTION

Dengue is the most common vector-borne acute infectious viral disease in the world. It is caused by one of the four serotypes of dengue virus (DEN-1, DEN-2, DEN-3, DEN-4) members of the genus *Flavivirus* in the family *Flaviviridae*.⁽¹⁻³⁾ Transmission to humans occurs through the bite of an infected female *Aedes aegypti*. This mosquito, a domestic species adapted to urban conditions, is the main vector in Brazil.⁽⁴⁾ Infection with one serotype confers permanent or long-term immunity. Therefore, the patient infected by a serotype, is susceptible to infection by another serotype, so care should always be taken during each epidemic and throughout the year.^(5,6) Its evolution can range from a mild, non-specific febrile syndrome to classic dengue fever (DF), to the severe forms of the disease, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).⁽⁷⁾

This disease is endemic in many countries throughout the tropical and subtropical range with over 100 million cases and

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24 thousand deaths per year worldwide.^(8,9) In Brazil, there have been epidemics of dengue reports since 1846 in São Paulo and Rio de Janeiro. In 1990, DEN-2 serotype was first isolated in the city of Niterói (RJ). With the circulation of two serotypes (DEN-1 and DEN-2), came the first reports of DHF. During the first 2 years of the 1990s, the incidence of the disease has remained almost entirely restricted to the states of Rio de Janeiro, Ceará, Pernambuco and Alagoas, but in subsequent years it quickly spread to other states.^(4,9)

In July 2010, the DEN-4 resurfaced in Roraima state after about 30 years of their last outbreak. From this epidemiological event the virus spread throughout the country. The non-detection of the virus for many years in Brazil left vulnerable most of the population to its reappearance. Shortly after, a major dengue epidemic began in the country by a serotype little known previously. At the beginning of 2013, the DEN-4 was detected in the city of Campos dos Goytacazes (RJ), Brazil, starting the largest dengue epidemic ever faced by the city.^(10,11)

Dengue is a reportable disease, since, from the suspicion, one can carry out an investigation of the probable site of infection and, if necessary, take preventive measures, particularly with respect to the vector.^(12,13) The symptoms are usually presented as mainly with chills, headache, retroocular pain, body pain and arthralgia in 90% of cases, accompanied by nausea or vomiting and a skin rash like measles that last 2 to 7 days in about 60% of cases. There may also be a sharp pain in muscles and joints with the feeling, as if the bones were breaking, also called “breaks bones fever”.⁽¹⁴⁾

However, a small proportion of patients may have exacerbated symptoms and progress to severe forms of the disease such as DHF and DSS, both characterized by important vascular leakage, thrombocytopenia and hemorrhagic manifestations. Infection with one serotype results in permanent immunity to that serotype, but only gives a short-term immunity to other serotypes. In fact, the severe forms of the disease are most often found in individuals experiencing a secondary infection by a different serotype.^(15,16)

Although the dengue virus is not a hepatotropic virus itself, liver damage due to dengue infection is not uncommon and has been reported since 1960. In dengue infection, the degree of liver dysfunction ranges from mild injury with isolated elevation of aminotransferase to injuries with severe jaundice and fulminant hepatic failure. Hepatic dysfunction may be a direct viral effect or an adverse consequence of the host immune response against the virus exacerbated.⁽¹⁷⁾ The inflammatory process resulting from dengue virus infection leads to a parenchymal injury that releases those enzymes in the plasma. In the acute phase of the disease, there is an increase in the aminotransferase levels, which subsequently decreases as the liver recovers.^(7,18,19)

Liver involvement can be characterized by symptoms of acute hepatitis, with pain in the right upper quadrant, hepatomegaly, jaundice and elevated levels of aminotransferases. Although the liver is not the main target organ of this disease, results of histopathological studies in patients with DHF and DSS revealed centrilobular necrosis, fatty changes, hyperplasia of Kupffer cells, acidophilus bodies and infiltration of the portal tract monocytes. In most cases, liver involvement prolonged

clinical course of this self-limited viral infection, but does not constitute a bad prognostic sign.^(18,20,21)

There are other factors that contribute to such dysfunction, including: race, diabetes, hemoglobinopathies, pre-existing liver damage and the use of hepatotoxic drugs. Although there are isolated case reports of fulminant hepatic failure, the setbacks in aminotransferases are generally mild and self-limited. Predictive factors for liver injury were identified, including DHF, secondary infection, thrombocytopenia, hemoconcentration, women and children.⁽⁸⁾

The diagnosis of dengue is performed based on clinical, epidemiological and laboratory data. Among the laboratory tests, the most dengue characteristic changes include leukopenia associated with lymphocytosis with atypical lymphocytes, thrombocytopenia and sometimes hemoconcentration. Of biochemical variables, the most frequent changes occur in liver function tests, as in aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase and alkaline phosphatase and serum albumin concentrations.^(4,19,22) Previous reports show that approximately 80% of patients with dengue have elevated liver enzymes, AST and/or ALT, which can be used as an early indicator of disease.⁽²³⁾

METHODS

Study design

This study is a cross-sectional analysis, retrospective, held in Center Reference Dengue (CRD) located in the city of Campos dos Goytacazes. We evaluated the records of 23,619 patients seen in the CRD from January to June 2013. The laboratory data used as a source of study are from samples collected after the first medical evaluation and attached to the records of patients. Patient charts were selected from both sexes, all ages, whose diagnosis of dengue was confirmed by IgM anti-dengue serology. The records of patients with negative serology or with clinical and laboratory information incomplete were excluded.

Definition of cases

Dengue cases were defined as individuals with epidemiological history and signs and symptoms. According to the guidelines of the World Health Organization (WHO), dengue should be suspected in cases of high fever (40°C/104°F) accompanied by two or more of the following symptoms: severe headache, pain behind the eyes, myalgia, arthralgia, nausea, vomiting, swollen glands or rash.⁽¹⁶⁾

Warning signs are severe abdominal pain, persistent vomiting, edema, tachypnea, fatigue, mucosal bleeding, lethargy or restlessness, increased liver greater than 2cm, increased hematocrit (Ht) associated with a rapid decrease in platelet count. There are also those of dengue severity criteria, namely: shock, fluid accumulation with respiratory distress, severe bleeding, liver alterations (AST or ALT greater than 1,000U/L), altered level of consciousness, cardiac involvement and other organs.⁽¹⁶⁾

Laboratory methods and variables analyzed

In the first medical visit, individuals who presented with clinical and epidemiological indications of dengue were reported

to the laboratory for collection of peripheral blood and the following laboratory tests were performed: complete blood count (CBC), erythrocyte sedimentation rate (ESR), AST and ALT). The tests were conducted in a laboratory associated to CRD and the reference values followed were those proposed by the laboratory. Ht parameters used to evaluate hemoconcentration included: adult man with a Ht >45%, old woman with a Ht >40% and children under 12 years with Ht >38%. Leukopenia was defined as the white blood cell count <4,000/ μ L and thrombocytopenia were defined as a platelet count <150,000/ μ L. The result of ESR >20mm/h was considered high.

The liver involvement was evaluated and classified these patients from the dosage of serum AST and ALT. According to the aminotransferase values, patients were classified into four groups. The reference values adopted for males were AST 59IU/L and ALT 72IU/L and for females AST 36IU/L and ALT 52IU/L.

The classification used for the aminotransferase levels were the same proposals in previous works by the same author.^(7,18,19) The normal results were classified as grade A, the values presented to three times higher than normal Grade B. In Grade C the values are between three and ten times upper limits of normal (ULN). In Grade D, values greater than ten times ULN, defining the hepatitis by virus serotype 4. In the present study, patients with aminotransferases ten times greater than the reference value were tested for Hepatitis A, B and C using the polymerase chain reaction (PCR) test. In this cases where the diagnosis of dengue was eliminated, other diagnostic hypothesis were investigated individually.

All cases of dengue were confirmed in the laboratory by the following: serological tests using enzyme immunoassay (ELISA PANBIO® for anti-DENV IgM) capture anti-dengue IgM in blood collected between days 5 to 10 after the first symptoms of fever.

Treatment

Patients with clinical features of dengue were seen at the outpatient clinic of the CRD and were conducted in accordance with the severity of the condition. Those without alarming clinical signs received information about the warning signs and need to return the unit, as well as symptomatic treatment associated with oral rehydration therapy.

Cases that, upon examination showed alarm signals received symptomatic treatment and intravenous rehydration, remained under medical observation. The following were reevaluated and released with directions or admitted to the CRD support hospital (*Hospital Plantadores de Cana*) to receive the appropriate clinical and laboratory monitoring.

Statistical analysis

The results were sorted and analyzed with the IBM Statistical Package for the Social Science (SPSS) Statistics 22 for Windows program, using the chi-square test to compare nominal variables, the Mann-Whitney U test for ordinal categorical variables and t-test for the significance of different means between different

groups. Variables with a p-value less than 0.05 were to be significant.

RESULTS

Among the patients treated at the CRD in the period of January to June 2013, 5,310 (22.48%) of the 23,619 cases had clinical findings and were serologically confirmed by IgM positive anti-dengue. Among these positive IgM patients, 1,714 (32.28%) were excluded from the analysis due to lack of sufficient laboratory data for inclusion in the research protocol. Thus, 3,596 (67.72%) patients with positive serology for dengue and characteristic symptoms were analyzed. The average age of patients was 37.5 years (\pm 17.1) and the group aged more affected by the disease was between 31 and 40 years (Figure 1). Regarding gender, 67.1% (2,412) were female. The diagnosis of DF was made in 98.9% (3,557) of individuals and of DHF in 1.1% (39). During this period were performed 224 (6.2%) hospitalizations.

The (CBC) showed the average (Ht) of 40.82% (\pm 3.82), mean platelet 192,254.95/ mm^3 (\pm 69,026.22) and average leukocyte 4,555.76/ mm^3 (\pm 1,997.33).

With regard to laboratory abnormalities, 1,677 patients (46.6%) were identified with leukopenia, 1,523 (42.4%) had hemoconcentration, 976 (27.1%) had thrombocytopenia and 393 (10.9%) were diagnosed with hemoconcentration and concomitant thrombocytopenia.

Of the total patients studied, 49.2% (1,768) had normal aminotransferase levels (grade A), 43.4% (1,559) had changes in aminotransferase levels by up to 3 times the upper limit of normal (grade B), 7.0% (253) had elevations in aminotransferase level three times the reference value (grade C) and 0.4% (16) developed acute hepatitis (grade D) (Table 1). The degree of change in aminotransferases was significantly higher among women ($p < 0.05$) (Table 1). It was also observed that the patients had thrombocytopenia and hemoconcentration major changes in the levels of aminotransferases ($p < 0.05$) (Table 1).

The average AST and ALT levels were higher in dengue hemorrhagic type (147.51IU/L and 111.54 \pm 137.74IU/L \pm 81.27, respectively) as compared to DF (55.18IU/L and 60.39 \pm 52.06IU/L \pm 57.50, respectively) ($p < 0.05$) (Table 2).

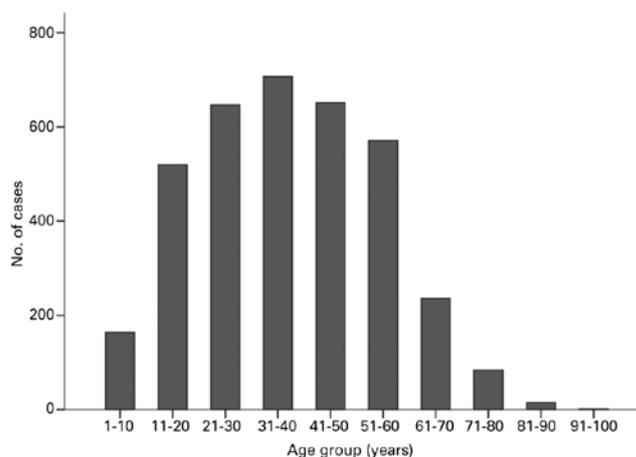


Figure 1. Age distribution of study.

Table 1. Comparative analysis between groups of enzyme classification, gender and thrombocytopenia/hemoconcentration

	Grade A 49.2% (1,768)	Grade B 43.4% (1,559)	Grade C 7.0% (253)	Grade D 0.4% (16)	Total 100% (3,596)
Gender					
Female	39,6% (954)	51,0% (1,229)	8,8% (213)	0,7% (16)	67,1% (2,412)
Male	68,8% (814)	27,9% (330)	3,4% (40)	0,0% (0)	32,9% (1,184)
<i>p</i> <0.05					
TCP + HCT*					
No	51,2% (1,639)	42,1% (1350)	6,3% (202)	0,4% (12)	89,1% (3,203)
Yes	32,8% (129)	53,2% (209)	13,0% (51)	1,0% (4)	10,9% (393)
<i>p</i> <0.05					

*TCP: thrombocytopenia; HCT: hemoconcentration.

Table 2. Aminotransferase average of 3,596 patients analyzed and its correlation with sex, dengue classification, thrombocytopenia/hemoconcentration, hematocrit, platelets, leukocytes and hospitalization

	AST (IC:95%)	ALT (IC:95%)
Average	56.18 (±54.53)	60.94 (±58.04)
Levels		
Normal	52.9% (n=1,904)	68.2% (n=2,454)
Abnormal (<3 x)	40.5% (n=1,457)	27.9% (n=1,003)
>3 x	6.1% (n=220)	3.8% (n=135)
>10 x	0.4% (n=15)	0.1% (n=4)
<i>p</i> <0.05		
Gender		
Female	56.58 (±56.72)	60.88 (±60.31)
Male	55.38 (±49.79)	61.08 (±53.14)
<i>p</i> =NS		
Dengue		
Classic	55.18 (±52.06)	60.39 (±57.50)
Haemorrhagic	147.51(±137.74)	111.54 (±81.27)
<i>p</i> <0.05		
TCP+HCT*		

IC 95%: confidence interval; TCP: thrombocytopenia; HCT: hemoconcentration.

Among patients who presented with leukopenia, their aminotransferases average was lower (AST 52.65IU/L±50.51 and 52.81 ALT IU/L±47.99) compared to individuals without any drop in overall white blood cell count (59.27 AST IU/L and ALT 68.05±57.65IU/L±64.75) (*p*<0.05) (Table 2).

Of the total patients studied, 224 were submitted to hospitalization, with the AST average of 88.18IU/L (±100.47) and ALT 77.95 IU/L (±88.38), which is higher than the average AST and ALT in ambulatory patients (*p*<0.05) (Table 2).

DISCUSSION

The etiology of elevated aminotransferases levels during acute Dengue is not clear, since the AST is expressed in other organs than the liver, including heart, skeletal muscle, red blood cells,

kidneys and brain. ALT is mainly secreted by liver,^(17,24) justifying the greatest number of changes to the AST enzyme, represented by the lower number of values classified within normal limits (grade A), when compared with the enzyme ALT changes.

In this study, the change of aminotransferases was lower both in number of patients and in degree of involvement compared to other works by the same author addressing the DENV-3.^(7,18) Thus, it is quite clear that the DENV-4 has less capacity to liver damage when compared with the DENV-3.

Despite the lower liver involvement by DENV-4, it was still a significant number of patients with altered levels of aminotransferases, requiring clinical laboratory monitoring for an extended period.

A significant correlation between global leukocyte count and changes of enzymes, in which the aminotransferase levels were higher in the presence of leukocytosis, was observed in this study. This suggests that there is an immune-mediated response able to damage tissues expressing aminotransferases and therefore increase these enzymes in blood plasma. Larger studies are needed to confirm this event and its clinical correlation.

The elevation of AST and ALT was more relevant in female patients. This fact was corroborated by the literature, showing that women are more susceptible to enzymatic changes and therefore constitute a risk group. So it becomes evident the importance of new studies on the clinical significance and the pathophysiology of this event.

Dengue infection can cause acute damage in extra hepatic tissues expressing AST. Increased levels of aminotransferases may not be entirely due to severe hepatic involvement. Therefore, it is possible that patients with high levels of AST were also more likely to be classified as severe dengue, according to the criteria of 2009 WHO⁽¹⁶⁾ though there was no association with poor prognosis.

CONCLUSION

The evolution of liver involvement in dengue is usually benign and self-limited, but cases of acute hepatitis may occur in some patients. Earlier studies by the author of this study indicated that infection with DENV-3 is related to the greater number of patients with abnormal liver enzymes compared with this study referring to the DENV-4 subtype.

However, it is important to pay attention to the use of hepatotoxic drugs, which can aggravate the hepatic involvement in some cases, and thus possibly change the benign prognosis of the disease in most cases.

Despite dengue's pathogenesis is a much-studied subject, some mechanisms have not been fully elucidated, as the real role of cytokines in liver tissue damage, extra hepatic and clinical in general. Further studies are needed to understand these mechanisms and their application in daily practice.

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