Revista da Sociedade Brasileira de Medicina Tropical 45(6):675-681, Nov-Dec, 2012

Major Article

Clinical and hepatic evaluation in adult dengue patients: a prospective two-month cohort study

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ABSTRACT

Introduction: To analyze the liver dysfunction and evolution of signs and symptoms in adult dengue patients during a two-month follow-up period. **Methods:** A prospective cohort study was conducted in Campos dos Goytacazes, Rio de Janeiro, Brazil, from January to July, 2008. The evolution of laboratory and clinical manifestations of 90 adult dengue patients was evaluated in five scheduled visits within a two-month follow-up period. Twenty controls were enrolled for the analysis of liver function. Patients with hepatitis B, hepatitis C, those known to be human immunodeficiency virus (HIV) seropositive and pregnant women were excluded from the study. **Results:** At the end of the second month following diagnosis, we observed that symptoms persisted in 33.3% (30/90) of dengue patients. We also observed that, 57.7% (15/26) of the symptoms persisted at the end of the second month. The most persistent symptoms were arthralgia, fatigue, weakness, adynamia, anorexia, taste alteration, and hair loss. Prior dengue virus (DENV) infection did not predispose patients to a longer duration of symptoms. Among hepatic functions, transaminases had the most remarkable elevation and in some cases remained elevated up to the second month after the disease onset. Alanine aminotransferase (ALT) levels overcame aspartate aminotransferase (AST) during the convalescent period. Male patients were more severely affected than females. **Conclusions:** Dengue fever may present a wide number of symptoms and elevated liver transaminases at the end of the second month.

Keywords*:* Dengue. Hepatic dysfunction. Persistence of symptoms. Prospective cohort.

INTRODUCTION

Dengue is the most important arboviruses disease, affecting increasing numbers of individuals and countries every year. Approximately 2.5 billion people live in dengue endemic areas and the number of new cases every year is estimated in 50 million[1]. The disease predominates in urban centers of tropical regions of developing countries[2,3], where environmental conditions favor the proliferation of its vector, the *Aedes aegypti*[4], while social and economic issues facilitate disease dissemination. Altogether this turns dengue into one of the main public health problems in the world[1].

In the last decades, Latin America has faced a dramatic increase in dengue incidence[2]. Brazil has suffered many epidemics with severe forms of the disease and currently accounts for more than 70% of the reported cases in the Americas[5].

When symptomatic, the illness can range from a mild to a severe form and eventually death may occur, which in most cases is preceded by shock[6]. The main mechanism leading to shock is the plasma leakage that occurs due to increased microvascular permeability[6,7]. Any one of the four serotypes known (DENV 1 to 4) can cause any form of dengue[6].

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Received in 27/12/2011
Accepted in 04/07/2012

Dengue is marked by a broad range of clinical signs and symptoms. The most remarkable laboratorial changes are leukopenia with lymphocytosis, thrombocytopenia, and hemoconcentration, the latter occurring in some cases, usually when associated with more severe dengue[1]. Hepatic dysfuntion is also a frequent and important finding[8,9] and hepatitis can eventually occur[10,11].

Since its recognition as a disease, dengue has mostly been considered an acute self-limiting disease and has been described as an acute febrile disease[6] that usually does not last more than one to two weeks[12]. Nevertheless in 1997 the World Health Organization (WHO) alluded to the possibility of a persistent fatigue in dengue patients[6] confirmed later by Seet and colleagues[13]. The persistence of myositis after dengue infection has been reported[14] but only a few studies have prospectively assessed the persistence of signals and symptoms in adult dengue patients[15] as well as the persistence of liver enzyme alterations[16,17]. Considering the magnitude of dengue epidemics each year and the possibility of the persistence of signs and symptoms due to this disease, our aim was to analyze prospectively the liver dysfunction and evolution of a wide range of signs and symptoms in adult dengue patients during a two-month follow-up period.

METHODS

Study design and population

A prospective cohort study was conducted at the Dengue Reference Center (CRD) in the City of Campos dos Goytacazes in the State of Rio de Janeiro, Brazil, from January to July 2008.

Individuals aged 18 years or older who presented acute febrile illness within the first 5 days from the onset of a fever that initially fit in the case definition for probable dengue according to WHO[6] were invited to participate in the study. The exclusion criteria were patients who turned out to be positive for hepatitis B or C, pregnant women, and patients with a known human immunodeficiency virus (HIV) positive serology. Also were excluded patients who did not attend the first and the last visit. Twenty controls, composed of patients suspected of having dengue who presented at CRD with acute febrile illness and whose dengue diagnosis was excluded by specific laboratorial exams, were enrolled for the analysis of liver function. The exclusion criteria for the control group were the same as adopted for dengue patients.

The laboratory diagnosis was based on the detection of non-structural antigen 1 (NS1) dengue antigen for samples within the first 5 days from the onset of fever. From the 6th day up to the second week immunoglobulin M (IgM) was performed in all patients. In order to confirm some questionable cases it was also considered dengue patients those with a four-fold increase in the immunoglobulin G (IgG) titer between two samples collected two weeks apart. The polymerase chain reaction (PCR) assay was performed in 30 patients to investigate the dengue serotype prevalence.

Data collection

Standardized forms, were used to collect clinical and epidemiological data obtained in five scheduled visits that occurred during a two-month follow up: within the first five days from the onset of the disease and at 8, 15, 30, and 60 days after the beginning of the symptoms. In the standardized form, there were included 26 signs and symptoms that were systematically evaluated in each visit as well as a complete clinical examination and the following laboratory assays, that were performed using blood samples: hemogram, aspartate aminotransferase (AST), alanine aminotransferase (ALT), direct and indirect bilirubin, prothrombin time (PT), and creatine kinase (CK). In the first visit, hepatitis B surface antigen (HBsAg) and anti-hepatitis C virus (HCV) were requested for all patients to screen for hepatitis B and C respectively.

The reference values for liver enzymes were established by the manufacturer (Johnson & Johnson Inc., Rochester, NY,USA), defined as follows: for men, AST values were up to 59U/L and ALT up to 72U/L. For women, AST values were up to 36U/L and ALT up to 52U/L. The reference values for CK were up to 170U/l for men and up to 135U/L for women. For both genders, the reference values for direct and indirect bilirubin were 0.4mg/dl and 0.8mg/dl respectively.

Laboratory methods

The hemogram, AST, ALT, PT, CK, HBsAg, and anti-HCV were performed in a private clinical analysis laboratory affiliated with the Brazilian Society of Clinical Analyses.

Reverse transcriptase-polymerase chain reaction (RT-PCR): The viral RNA was extracted from the acute-phase sera and it was performed according to Lanciotti et al.[18,19].

Serology: A dengue IgM-capture enzyme-linked immunosorbent assay (ELISA) was performed according to manufacturer's instructions (Pan Bio®, Brisbane, Australia). IgG-ELISA was performed as described by Miagostovich et al.[20].

NS1 antigen capture assays: NS1 was performed in the acute-phase sera, according to manufacturer's instructions (Pan Bio® rapid strip test kits, Bribane, Australia).

Severity dengue case classification

Dengue cases were classified as dengue without warning signs, dengue with warning signs, and severe dengue according to WHO[1]. The warning signs included abdominal pain or tenderness, persistent vomiting, mucosal bleeding, lethargy, restlessness, liver enlargement (>2 cm), and increase in hematocrit concurrent with rapid decrease in platelet numbers. Patients were considered as having severe dengue when during the course of the disease they presented any of the following: 1) plasma leakage that may lead to dengue shock (systolic arterial pressure < 90 mmHg with signs of poor capillary perfusion) and/or fluid accumulation; 2) severe bleeding (bleeding that leads to hemodynamic instability or is sufficient to consider blood transfusion); 3) hepatitis (AST or ALT more than 10-fold the normal limit), encephalopathy (impaired consciousness, seizures), myocarditis, or the severe impairment of any other organ.

Statistical analysis

The statistical analyses were performed using the SPSS 16.0 (Statistical Package for the Social Sciences Inc., Chicago, IL, USA). For continuous variables, the Mann-Whitney U test, Wilcoxon test and Student t test were used. The X^2 (Chi-square) test was used for categorical variables and when an expected value was less than 5, the Fisher's exact test was used. To assess the difference among more than two groups, the Kruskal-Wallis test was used. Correlation was estimated by Spearman's test.

To demonstrate hepatic transaminases comparing dengue patients with control group, a local regression method was used: Loess (locally weighted scatterplot smoothing) using the statistical program *R* (version 2.11.0).

For all tests, a 95% confidence interval was assumed with a significance of 5%.

Ethical considerations

This study was approved by the Research Ethics Committee of the School of Superior Sciences of *Santa Casa de Misericórdia de Vitória*, State of Espírito Santo, Brazil.

RESULTS

Among the 186 enrolled patients, 76 patients were excluded (2 were pregnant, 2 had positive Anti-HCV, and 72 did not complete the follow-up). The sample loss in both groups showed no statistical difference. Thus, 90 dengue patients and 20 controls were included with a general sample mean of 3.68 per patient (3.7 for dengue patients and 3.5 for controls).

The following variables were equally distributed in both groups: acetaminophen use to control symptoms, gender, age, and alcohol consumption.

The average age of dengue patients was 35.84 (standard deviation; SD 12.69) while it was 33.40 (SD 10.73) in controls (p=0.426, Student t test). Females accounted for 52.2% (47/90) of dengue patients and 60% (12/20) of the control group. There was no difference between genders in both groups (p=0.528, chi-square). Thirty-one (34.4%) dengue patients reported some level of alcohol consumption, while alcohol consumption was reported by 6 (30%) individuals in the control group (p=0.811, chi-square). There was

no abusive alcohol consumption reported in either group. Alcohol consumption was higher in males when compared to females (p=0.027). No difference was observed for acetaminophen intake (p=0.169, chi-square).

To assess the serotype prevalence, PCR was performed in 30 out of the NS1-positive patients throughout the 6 months of the study period. Among these 24 were positive, all of them for dengue virus 3 (DENV-3).

At the end of the first and second month we observed that 57.8% (52/90) and 33.3% (30/90) of dengue patients respectively, complained of at least one sign or symptom.

Table 1 shows the analysis of dengue clinical symptoms in relation to the onset of disease and the two-month follow-up **(Table 1).**

As observed in **Table 1**, 15 out of 26 symptoms were present at days 30 and 60. There was a decline in the symptom ratio from the first week on, except for pruritus, which had a peak at day 8, and hair loss, which more patients presented during the second month. Additionally we observed that the platelet number up to day 8 was significantly lower in patients with bleeding but no association was found between this sign and PT values (Mann-Whitney test).

Significant differences among the three severity groups were observed in the duration of anorexia and taste alteration, as shown in **Table 2.** Further analyses of these symptoms, considering two severity groups each time, showed that for both symptoms the severe dengue group presented longer duration when compared with the dengue without warning signs group (p<0.05, Mann Whitney test). Only anorexia was shown to persist longer in severe dengue patients, as compared to dengue with warning signs (p=0.04, Mann-Whitney test). Previous DENV infection was not associated with longer duration of any of the 26 signs and symptoms analyzed**.**

Table 3 summarizes the symptoms that may not initiate at the same time as fever. The amplitude of the onset of the symptoms is very wide and some of them, such as hand/foot edema, hair loss, and paresthesia can begin at one month or even later.

When results were stratified by gender, we observed higher transaminase levels in males than in females. Transaminases kept within normal levels in the control group **(Figure 1).**

The percentage of elevated AST or/and ALT levels reached 40.7% (22/54) (at day 30 and 7.6% (6/79) at day 60 in dengue patients. Stratified by gender, 11.8% (4/34) had one of the two

TABLE 1 - Signs and symptoms observed at different moments during the two-month follow-up period in 90 dengue patients, Campos dos Goytacazes, State of Rio de Janeiro, Brazil, 2008.

	Acute phase (≤ 5 days)		Days after onset of disease								Accumulated frequency in 2 months	
			8		15		30		60			
Variables	n	%	n	%	n	%	n	%	n	%	n	%
Fever	90	100.0	1	1.1	0	0.0	0	0.0	0	0.0	90	100.0
Chills	70	77.8	6	6.7	1	1.1	0	0.0	0	0.0	72	80.0
Headache	87	96.7	24	26.7	11	12.2	3	3.3	2	2.2	89	98.9
Retro orbital pain	72	80.0	21	23.3	8	8.9	2	2.2	2	2.2	72	80.0
Myalgia	86	95.6	34	37.8	12	13.3	11	12.2	5	5.6	86	95.6
Arthralgia	69	76.7	28	31.1	19	21.1	12	13.3	10	11.1	69	76.7
Adynamia	87	96.7	65	72.2	47	52.2	30	33.3	19	21.1	89	98.9
Weakness	85	94.4	53	58.9	34	37.8	23	25.6	15	16.7	85	94.4
Fatigue	83	92.2	56	62.2	42	46.7	28	31.1	18	20.0	84	93.3
Anorexia	82	91.1	60	66.7	34	37.8	20	22.2	11	12.2	83	92.2
Taste alteration	80	88.9	47	52.2	23	25.6	14	15.6	8	8.9	80	88.9
Nausea	77	85.6	34	37.8	11	12.2	3	3.3	3	3.3	77	85.6
Vomiting	38	42.2	3	3.3	1	1.1	0	0.0	0	0.0	37	41.1
Diarrhea	25	27.8	12	13.3	2	2.2	0	0.0	0	0.0	32	35.6
Exanthema	32	35.6	30	33.3	3	3.3	0	0.0	0	0.0	41	45.6
Pruritus	37	41.1	50	55.6	14	16.6	4	4.4	4	4.4	69	76.7
Dizziness	65	72.2	27	30.0	7	7.8	3	3.3	2	2.2	66	73.3
Cough	33	36.7	15	16.7	11	12.2	6	6.7	4	4.4	37	41.7
Runny nose	11	12.2	6	6.7	3	3.3	1	1.1	0	0.0	11	12.2
Edema	11	12.2	7	7.8	2	2.2	0	0.0	0	0.0	12	13.3
Hair loss	7	7.8	8	8.9	11	12.2	12	13.3	14	15.6	17	18.9
Paresthesia	16	17.8	6	6.7	4	4.4	3	3.3	3	3.3	18	20.0
Bleeding	18	20.0	14	15.6	3	3.3	0	0.0	0	0.0	24	26.7
Photophobia	35	38.9	12	13.3	1	1.1	0	0.0	0	0.0	36	40.0
Abdominal pain	33	36.6	15	23.3	3	3.3	0	0.0	0	0.0	33	36.6
Hypotension	36	40.0	3	3.3	0	0.0	0	0.0	0	0.0	49	54.4

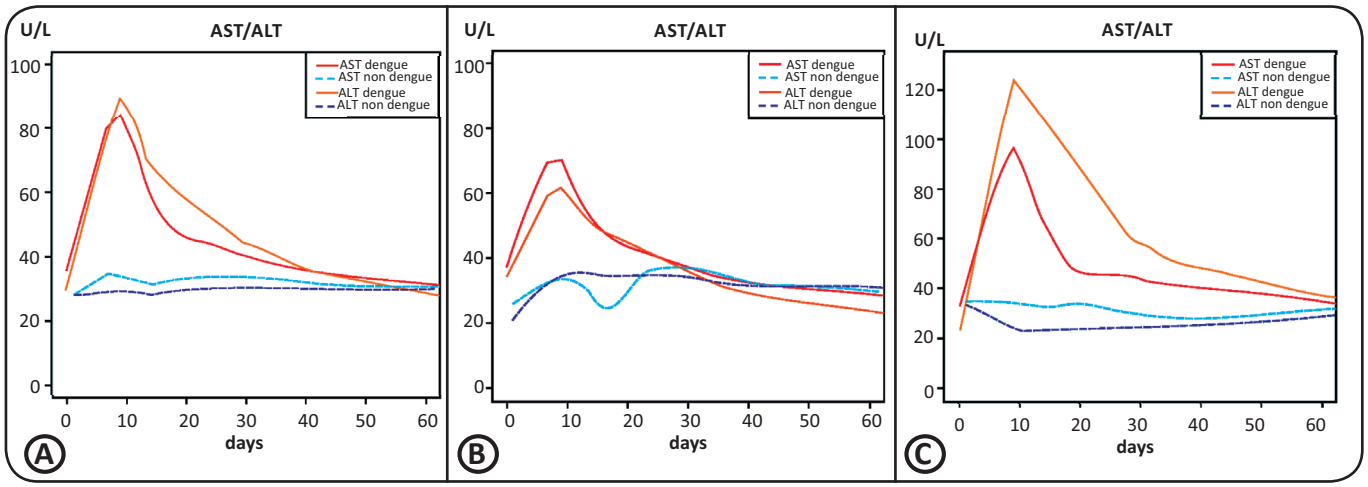

FIGURE 1 - Evolution of the levels of the hepatic enzymes in dengue patients, compared to a control group during a two-months follow-up period, using loess method: A) Total sample; B) Female; and C) Male. AST: aspartate aminotransferase; **ALT:** alanine aminotransferase.

TABLE 2 - Median duration of the signs and symptoms among patients, according to the level of severity.

Variables	Dengue (n=28)	Dengue with warning signs (n=49)	Severe dengue (n=13)	Difference among
	Mdn (IQR)	Mdn (IQR)	Mdn (IQR)	groups[a]
Fever	4 (3.25-5)	4 (3-5)	4 (3-5)	0.794
Chills	2 (1-4)	3 (2-4)	2 (1-4)	0.182
Headache	4 (3-6)	5 (3-8)	4 (2.5-8)	0.188
Retro orbital pain	4 (3-6)	5 (4-8)	4 (2.5-5.5)	0.205
Myalgia	6 (3.5-8)	6 (4-9.75)	6 (4-9.5)	0.541
Arthralgia	6 (5-8)	6 (4-27.5)	6 (4-11.5)	0.826
Adynamia	9 (6-30)	15 (7-30)	30 (5.5-60)	0.421
Weakness	7.5 (5.25-11)	10.5 (6-30)	15 (6-60)	0.158
Fatigue	6 (5-27)	12 (1-30)	15 (5.5-60)	0.256
Anorexia	8.5 (5.25-12)	9 (6-23.5)	15 (8.5-60)	0.036*
Taste alteration	6 (3.5-10.5)	9 (11.51)	13 (24.14)	0.023*
Nausea	5 / (3-8.25)	5 (3-9)	4 (2.25-6.75)	0.879
Vomiting	1.5 (1-2.25)	2 (1-3)	4 (1-5.5)	0.285
Diarrhea	2 (2-3)	2 (1-4)	3.5 (1.25-8.5)	0.398
Exanthema	5 (3-9)	4.5 (3-7)	5 (2-7.25)	0.893
Pruritus	4 (2-8.5)	4 (2-7)	5 (2.75-5.75)	0.899
Dizziness	3 (2-5)	6 (3-8.25)	4 (2.25-10.25)	0.177
Cough	2 (2-10)	5 (2-8)	15 (4-30)	0.062
Hand or foot edema	5 (3-7)	4 (3.5-30)	7.5 (4-11)	0.637
Hair loss	30 (15-30)	37.5 (10.25-52.50)	30 (15-45)	0.830
Paresthesia	2 (2-6)	5 (2.5-6)	9.5 (2-45)	0.338
Bleeding	2 (1.5-6)	4 (2-5)	3 (1.25-5)	0.850
Photophobia	3.5 (2-7.5)	4.5 (3-7.25)	2 (2-3)	0.146

Mdn (IQR): median (interquartile range); [a]p-value, Kruskall-Wallis test. *p<0.05

transaminases elevated in the male group at day 60, whereas this occurred in only 4.4% (2/45) of the female group. Serum levels of AST showed a statistical difference between genders only at day 60, whereas ALT showed levels statistically higher in males at days 8, 15, 30 and 60 (p<0.05, Mann-Whitney test) **(Figure 2).**

In the analysis of other hepatic tests such as PT and, indirect and direct bilirubin, we did not observe any remarkable alteration in dengue patients, even in those with the severe form. In the acute phase and at day 8 the platelets were significant lower in patients who had some hemorrhagic manifestation (p<0.05, Mann-Whitney test); nonetheless there was no correlation between platelet levels and bleeding duration in any of the five measures (p>0.05, Spearman test).

The mean CK levels in the acute phase and at day 8 were higher when compared with the following next three phases in dengue patients (p=0.027 Wilcoxon test). However, we did not find any significant difference between CK in the dengue group and controls, at any of the different time points of the follow-up (Mann-Whitney test). We also observed a positive correlation between CK and AST

TABLE 3 - Appearance of signs and symptoms on the days following the onset of the disease.

Variables	Dengue without warning signs (n=28) Mdn (IQR)	Dengue with warning signs (n=49) Mdn (IQR)	Severe dengue (n=13) Mdn (IQR)	Difference among groups- p[a]	Amplitude
Nausea	1 (1-1)	1 (1-2)	2.5 (1-4)	0.089	1-8
Exanthema	4.5 (1.25)	4 (3.5-5)	2.5 (1.75-5)	0.426	1-13
Pruritus	5 (3-7)	5 (4-7)	5 (2.75-6.75)	0.781	1-13
Dizziness	1 (1-4)	1 (1-2)	1.5 (1-3.75)	0.478	1-9
Cough	1 (1-1)	2 (1-3)	1 (1-5.25)	0.060	1-9
Hand or foot edema	8 (4-30)	3 (3-3.5)	5 (2.5-9)	0.105	1-30
Hair loss	22 (5-30)	4 (1.5-50)	9 (8-30)	0.905	1-30
Paresthesia	3 (2-6.5)	1 (1-4)	4.5 (1-9)	0.399	1-45
Bleeding	4 (2-9.5)	4 (2.5-6)	4.5 (1-2)	0.814	1-12

Mdn (IQR): median (interquartile range); [a]p-value, Kruskall-Wallis test.

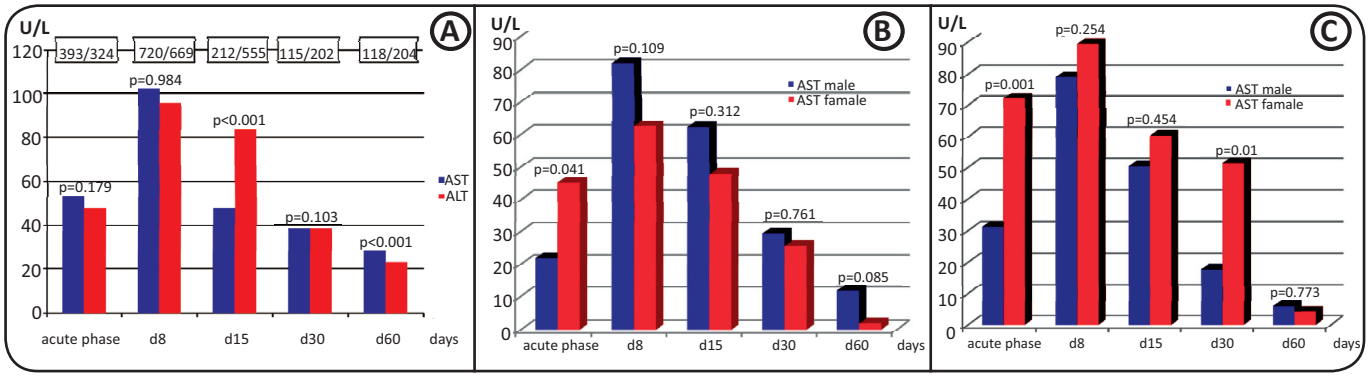

FIGURE 2 - Median of AST and ALT values of acute and follow-up phases in dengue patients. In the squares above the columns are the maximum values. Differences between transaminases in each point were assessed using Wilcoxon test (A). Percentage of dengue patients with elevated ALT at different phases of the follow-up, stratified by gender (B). Percentage of dengue patients with altered AST at different phases of the follow-up, stratified by gender. Differences between genders in each point were assessed using Chi-square test (C). AST: aspartate aminotransferase; **ALT:** alanine aminotransferase.

in the acute phase (p=0.007; r=0.636) and at day 8 (p=0.012; r=0.363) (Spearman test). In the analyses between CK and ALT we observed a positive correlation only at day 8 (p=0.006; r=0.398) (Spearman test).

DISCUSSION

The persistence of symptoms in dengue patients has only recently been studied. In this study, we recorded prospectively a wider range of signs and symptoms than other studies have done so far[13,15,21,22].

A considerable ratio of dengue patients presented some clinical manifestations at day 60. This ratio was higher when compared to that found in some studies[13,15] and smaller when compared to others[21,22]. These differences may be due to different methodologies applied in each study, different periods analyzed from the beginning of the illness onwards, number of variables analyzed, percentage of dengue severity in the sample, and all the variables that could impact the study outcome[23] such as virus virulence and patients' race and age.

Some symptoms such as fever, chills, headache, and vomiting had an abrupt decline after the acute phase. This was not observed for symptoms like adynamia, weakness, and fatigue. The most common symptoms found at days 30 and 60 were those related to fatigue syndrome such as adynamia, weakness, and fatigue although arthralgia, anorexia, and taste alteration reached around 10% and hair loss 15% at the end of the second month. In accordance with results found by Seet and colleagues[13], symptoms related to fatigue syndrome were present in about 20% of dengue patients at the end of 60 days. These symptoms did not show longer duration in severe dengue cases when compared to dengue cases with or without warning signs. In fact, only anorexia and taste alteration were found to have significant longer duration in the group of patients with severe dengue when compared to the groups for dengue with and without warning signs.

Hair loss could last more than three weeks in all dengue severity groups. This might be explained by a number of potential causes such as nutritional deficiencies, and physiologic and emotional stress[24].

A peculiar aspect of the disease is that at least eight symptoms may not be present when the patient starts to have fever. In some cases, these symptoms (hair loss, hand or foot edema, and paresthesia) may occur as late as one month from the onset of the disease. Exanthema, one of the main characteristics of dengue signs, takes approximately four days to appear, and may take up to 13 days. Importantly, if we consider that most of the studies were done with patients at the acute phase, it is possible that a significant percentage of patients with exanthema were missed. The pruritus usually coincides with the exanthema, but sometimes patients have only pruritus. Consistent with previous studies[25,26], we observed a higher ratio of patients with pruritus compared to rash. It is known that pruritus is a common manifestation of cholestatic hepatitis[27]. Despite the large percentage of patients with abnormal liver transaminases, we did not observe

significant increase in direct bilirubin levels, and therefore discarded the hepatic changes as a cause of pruritus. Hypothetically, dry skin, which eventually accompanies the infection, could be one of the factors that explain the higher percentage of patients with pruritus compared to rash.

Although some signs and symptoms such as exanthema and hair loss began earlier in patients with severe dengue, there was no significant difference when compared to the time of onset in these patients and in those patients with and without warning signs of dengue.

Previous studies have shown that a previous infection by predisposes to more severe disease[28-30]. We did not observe association of secondary infection with longer duration of the 26 signs and symptoms analyzed. As the severity of cases is based primarily on immunological changes, it is possible that the persistence of signs and symptoms in patients with dengue is also, but with distinct mechanisms.

In our study population, only DENV-3 was identified, and considering that different serotypes might affect the severity of the disease[31,32] we do not know if these results can be extrapolated to other serotypes.

Some variables such as gender, age, and use of acetaminophen, that could potentially affect the analyses, were well distributed between dengue group and controls ($p<0.05$). Race, an important variable that interferes with dengue severity[33,34] and possibly with the persistence of symptoms, was not taken into account because a precise race discrimination is very difficult to perform with the Brazilian population due to its high level of admixture.

It should be noted that several patients did not complete the study for different reasons. It is possible that asymptomatic patients abandoned the study more often than symptomatic patients thereby increasing the ratio of patients with prolonged symptoms.

Another important aspect of dengue is the impact it has on hepatic function. After liver infection occurs, a dengue-induced liver cell apoptosis is observed[35], which explains the high enzyme levels during viremia and on the days immediately after viremia. Most dengue patients had some degree of hepatic abnormality during the course of the disease. We observed that at days 30 and 60, the levels of transaminases were 40.7 and 7.6%, respectively. Both transaminases reached their highest levels by the 10th day after the onset of the disease, in accordance with the findings of Kuo and colleagues[36]. Previous studies have reported a higher mean of AST level as compared to ALT[9,36]. Trung and colleagues also observed consistently higher levels of AST in dengue patients, including those in the convalescent period[16.] In fact, our results demonstrated higher levels of AST until the eighth day, but at day 15 we observe that the median ALT levels showed significantly higher levels when compared to the AST, which is related to a slower decline in ALT rather than an increase in their levels. It is known that AST has a shorter half-life than ALT but usually it is no longer than two days[35]. Thus, this difference in half-life cannot completely explain the different evolution of both enzymes. Considering that we found a positive correlation between AST and CK in the first 8 days, it is possible that part of the AST analyzed during the first 8 days comes from muscle injuring, which would stop earlier than the hepatic aggression. This would not be observed for ALT as this enzyme is considered more specific to the liver than AST[37].

When we analyzed the liver enzymes according to sex, we found that liver involvement was more severe in men. Except for the acute phase, this group showed ALT levels higher in all measures over the two-month period when compared to the levels found in women. Although alcohol consumption may affect mainly AST[38], there was no difference in AST levels between genders, even though the number of men who used alcohol was higher ($p=0.027$). At this point, we do not have an explanation for the difference in ALT evolution observed between genders.

In analysis of abnormal transaminase levels stratified by gender, female patients presented significantly higher ratios of elevated transaminases (ALT and AST) up to the 5th day after the onset of the disease and also at day 30, when only the AST was considered. Considering that the transaminase levels in the acute phase for both transaminases and for AST at day 30 were not statistically different between genders, we can assume that in spite of a higher ratio of females with abnormal transaminases, these would rather be mild or moderate elevations.

We did not observe worse liver damage among patients who used acetaminophen compared with those who did not, maybe because this is associated with high doses of this medication[39], which was not reported by our patients.

The persistence of dengue symptoms as well as the persistence of hepatic changes might be affected by several variables such as those associated to the severity of the disease[40,41]. Recently a study observed that persistence of dengue signs and symptoms might be associated with autoimmunity markers[22]. Considering that the virus is circulating mostly during the first 5 days and that the persistence is much longer than this, it is plausible that immunological mechanisms would play an important role in the persistence of clinical symptoms and in hepatic injury.

Dengue fever presents a great number of relevant and persistent symptoms at the end of 60 days from the onset of the disease. Prior DENV infection did not predispose dengue patients to a longer duration in signs and symptoms.

The hepatic enzymes are the most affected as compared to other liver functions, and in spite of their gradual decline, they may still be altered up to the second month. ALT levels overcome AST during the convalescent stage. Male dengue patients were more severely affected than females although females presented higher percentage of abnormal hepatic transaminases in the acute phase, and also at day 30 considering only AST.

ACKNOWLEDGMENTS

We would like to thank the *Laboratório Plínio Bacelar* for kindly providing space for us to perform the initial evaluation of our samples.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FINANCIAL SUPPORT

Municipality of *Campos dos Goytacazes (Prefeitura Municipal de Campos dos Goytacazes), Rio de Janeiro* and *Fundação Oswaldo Cruz, Rio de Janeiro*.

ABSTRACT IN PORTUGUESE

Avaliação das alterações clínicas e hepáticas em pacientes adultos com dengue: estudo prospectivo em um período de dois meses

Introdução: Analisar prospectivamente a disfunção hepática e a evolução dos sinais e sintomas em pacientes adultos com dengue durante um período de dois meses. **Métodos:** Realizamos um estudo prospectivo em Campos dos Goytacazes, Rio de Janeiro, Brasil, de janeiro a julho de 2008. Foi avaliada a evolução das manifestações clínicas e laboratoriais em 90 pacientes adultos com dengue, em um período de dois meses. Vinte controles foram arrolados para análise da função hepática. Em ambos os grupos foram realizadas coletas de dados e sangue nos primeiros cinco dias da doença, e aos 8, 15, 30 e 60 dias após o início da doença. Foram excluídos pacientes com hepatite B, hepatite C, gestantes e aqueles sabidamente soropositivos para HIV. **Resultados**: No final do segundo mês do início da dengue, 33,3% (30/90) dos pacientes apresentaram persistência de pelo menos um sinal ou sintoma. Estavam presentes no final do segundo mês 57,7% (15/26) dos sinais ou sintomas. Os maiores percentuais de persistência foram: artralgia, adinamia, fraqueza, fadiga, anorexia, alteração do paladar e queda de cabelo. A infecção prévia pelo vírus da dengue (DENV) não predispôs a uma maior duração dos sintomas. Da função hepática, observamos alterações relevantes somente nos níveis das transaminases, que em alguns casos permaneceram elevados até o final do segundo mês. Os níveis de ALT ultrapassaram os de AST na convalescença. Homens apresentaram níveis mais elevados de transaminases quando comparados aos de mulheres. **Conclusões:** Dengue apresenta grande número de sintomas e transaminases elevadas no final do segundo mês de doença.

Palavras-chaves: Dengue. Disfunção hepática. Persistência de sintomas. Estudo prospectivo.

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