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Brief Original Article

Abnormalities in electrocardiographic ventricular repolarization in patients with dengue virus infection

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Abstract

Introduction: Dengue virus infection (DENV) is an arboviral disease that affects millions of people in many countries throughout the world every year. The disease is caused by the bite of a mosquito (Aedes aegypti and / or Aedes albopictus). The symptoms/signs observed in this arboviral disease are unspecific, and the blood count usually shows leukopenia and thrombocytopenia. Although ECG changes may be observed in DENV, little is known about parameters of ventricular repolarization in patients with this condition. Accordingly, the aim of this study was to evaluate the QTc and QT interval dispersion to detect ventricular repolarization changes in patients with DENV.

Methodology: Ninety-three consecutive patients seen during DENV epidemics in a small town with non-complicated DENV were included; 93 normal individuals served as controls. Clinical data, blood count and the 12-lead ECG were obtained from each individual.

Results: The QTc duration was higher in patients with DENV in comparison to controls. Furthermore, 5% of DENV patients had abnormal lengthening of the QTc interval. No difference regarding QT interval dispersion was observed between DENV patients and controls. No DENV patient had increased lengthening of the QT interval dispersion.

Conclusions: Myocardial repolarization changes do occur in patients with DENV. Having into account the potential impact of these changes on patients' outcome, and because 12-lead ECG is not routinely recommended in the setting of DENV in our country, we recommend that a 12-lead ECG be taken from each patient with this condition during DENV epidemics.

Key words: Dengue; QT; QTc.

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Introduction

About 390 million people are infected with dengue virus (DENV) each year in more than 100 countries in each continent, and 96 million (25%) develop a clinical picture consistent with DENV infection (DENV) [1]. DENV is caused by four different strains, which are transmitted by a bite of a mosquito (*Aedes aegypti* and/or *Aedes albopictus)* that develops in backwater of tropical countries [1-3].

The clinical picture of patients with DENV are fever, cutaneous rash, myalgia, arthralgia, lymphadenopathy, retro-ocular pain, headache, nausea, and vomiting. Blood count usually shows thrombocytopenia and/or leucopenia in about 25% of patients. A small number of patients develop serious complications such are bleeding, organ failure, and hypovolemic shock with cardiovascular collapse [3]. Heart involvement manifests by atrial and/or ventricular premature beats, heart blocks, bundle branch blocks, ST-T changes, myocarditis, pericardial effusions and ectopic ventricular beats [4-20]. DENV has a negative chronotropic effect on the myocardium [17].

Overall, the prevalence of myocarditis during an outbreak approaches 12% [10]. Cardiac dysfunction detected by either abnormal echocardiogram or increased troponin blood levels has been associated with the severity of plasma leakage in DENV with complications. It is important to emphasize that such alterations may occur even in asymptomatic patients preceding the appearance of the severity of DENV [11,12].

Lengthening of the QRS interval has been observed in a patient with Takotsubo Cardiomyopathy secondary to DENV [13,18,19]. As far as we know, however, an electrocardiographic survey during DENV epidemics in patients with non-complicated DENV has not previously been performed. Consequently, no abnormalities in ventricular repolarization have primarily been observed during DENV epidemics. In fact, a superb review published some years ago on the subject in this journal has failed to review abnormalities

in ventricular repolarization in patients with DENV [20]. Accordingly, the purpose of this investigation was to assess parameters of ventricular repolarization during an outbreak of patients with DENV.

Methodology

A DENV outbreak, serotype 1, emerged in Porto Ferreira, a town of 50,000 inhabitants located in São Paulo state countryside, Brazil, in January 2015. From February to March, 2015, a total of 2619 patients were diagnosed as having DENV. All patients were seen in the primary care setting, as recommended by Brazilian health authorities during DENV outbreak, which does not have facilities to provide standard laboratory tests, except for serology for DENV and routine blood count.

Patients with a presumptive diagnosis of DENV on clinical grounds (fever plus two symptoms: severe headache, retro-ocular pain, myalgia, arthralgia, nausea, vomiting, lymphadenopathy, cutaneous rash) and leukopenia/thrombocytopenia in blood count underwent 12-lead ECG. Age < 18 years was not a criterion for exclusion of the study. The Enzyme-linked Immunosorbent Assay (ELISA) method was used to make the diagnosis of DENV from the 6th day of the beginning of symptomatology onwards. Detection of viral antigens through the NS1 method was used to make the serological diagnosis of DENV in those patients in the first 5 days of the beginning of symptoms. Patients with DENV were clinically managed according to Brazilian guidelines for treatment of this condition, which are in accordance with World Health Organization (WHO) guidelines [1].

Ninety-three patients with a positive serology for DENV were enrolled; 93 asymptomatic individuals of the apparently normal population usually followed at the primary care service, matched by sex and age, served as controls. Forty (43%) men comprised the control group, whereas the DENV group was made up of 38 (41%) men. No patient had warning sign or severe dengue, according to WHO [1]. All patients gave informed consent to take part in the investigation, which was approved by the Health Department of Porto Ferreira town. The study was previously approved by the Ethics Committee of The National Ministry of Health as well as by the Ethics Committee of University of Ribeirão Preto (ethics committee approval: CAAE: 38854114.7.0000.5498). After the informed consent was obtained, the patients were included in the investigation.

We used a digital electrocardiograph, micromed wincardio record, model 5.0.0136, manufactured by MICROMED Biotecnologia LTDA (Brasilia, Brazil), which records the 12 electrocardiographic leads simultaneously. Two qualified cardiologists who operated independently subsequently analyzed each recording. The recorder was set at 25 mm/s paper speed and 10 mm/mV. In each ECG tracing, QT intervals were measured in each lead from the onset of the QRS complex to the end of the T wave. In the presence of a U wave, the QT interval was measured to the nadir between T and U waves. The QT interval was measured automatically.

The QTc was established according the Bazett's formula with the QT-interval and the RR-interval in milliseconds (msec), as previously described [21-25]. The QT interval dispersion was defined as the difference between the maximum and the minimum QT interval in at least five leads [24]. Parameters of the 12-lead ECG of patients with DENV were compared to controls, matched by sex and age. For the purpose of this study, the upper limit of the QT interval was 450 msec for woman and 470 msec for man. The upper limit of the QTC interval dispersion was 60 msec [26].

Statistical analysis

Data are given as means ± standard deviation. The student T test was used to compare continuous variables between DENV patients and controls. Differences between groups at a p value < 0,05 were considered statistically significant.

Results

On admission, mean age of DENV patients was 71 ± 14 years. Malaise was found in 90 (97%) of such patients, fever in 89 (96%), headache in 82 (88%), arthralgia in 77 (83%), retrocular pain in 70 (75%), nausea in 64 (69%), pruritus in 58 (63%), exanthema in 41 (44%), diarrhea in 38 (41%), vomiting in 25 (27%), abdominal pain in 24 (26%), and bleeding in 7 (13%). Systolic blood pressure was 118 ± 15.6 mmHg, and diastolic blood pressure 75 ± 11.3 mmHg. A positive tourniquet test was found in 19 patients (23%). Mean hemoglobin was 14 ± 1.4 g/dL, mean leucocytes count 3190 ± 1081 per mm^3, and mean platelet count 146568 ± 62042 per mm^3.

Table 1 summarizes the electrocardiographic parameters observed in DENV patients and in controls. No difference was found in electrocardiographic variables between DENV patients and controls, with the exception of QTc interval, which was slightly but significantly ($p < 0.05$) increased compared to controls (+ 4%). Furthermore, 5% patients with DENV had abnormal lengthening of the QTc interval. No abnormal lengthening of the QTC was observed in controls. No

Table 1. Electrocardiographic findings in patients with Dengue Viral Infection and controls.

Variables	DENV (n = 93)	Controls (n = 93)
Sinus tachycardia	4 (4%)	4 (4%)
Sinus bradycardia	2 (2%)	1 (1%)
Atrial fibrillation	1 (1%)	0 (0%0
Atrial flutter	0 (0%)	1 (1%)
Right bundle branch block	6 (6%)	9 (10%)
Left bundle branch block	1 (1%)	0 (0%)
Left ventricular hypertrophy	3 (3%)	3 (3%)
ST-T changes	2 (2%)	2 (2%)
QTc interval (msec)	407.4 ± 35.3	391.8 ± 35.5*
QT dispersion (msec)	40 ± 14.8	39.5 ± 16.6

*p = 0,00004; DENV = Dengue Viral Infection.

difference was observed in QT interval dispersion between controls and DENV patients. Because all patients had only minor DENV, they were discharged from the primary care service without a follow-up scheduled.

Discussion

This study shows that patients with DENV are found to have lengthening of the QTc interval, but not of the QT interval dispersion. Furthermore, about 5% of such patients showed increased QTc interval. Increased QT interval has previously been observed in a patient with Takatsubo cardiomyopathy secondary to DENV. This QT interval change was maintained for eight days, returning to normality without specific treatment [13]; such alteration was attributed to myocardial edema [14]. In this particular case, the abnormality in ventricular repolarization accompanied the appearance of acute cardiomyopathy. Thus, no primary ventricular repolarization alteration has been observed in patients with DENV. This investigation, therefore, adds to the knowledge of abnormalities in ventricular repolarization in patients with DENV.

The pathophysiological mechanism underlying our findings is still unclear. It is conceivable that myocarditis secondary to DENV might have played a role [14]. In fact, dengue viral invasion of the myocardium may lead to a massive cytokine release, which can result in severe myocardial injury, sometimes culminating in fulminant myocarditis [4]. Therefore, it is attractive to consider a mild cytokine-induced myocardial injury as the cause of ventricular repolarization observed in our study.

It is regrettable, however, that neither transthoracic echocardiogram nor troponin serum levels were available for our patients. This might further suggest the diagnosis of myocarditis in such patients. As mentioned earlier, such subsidiary exams are not routinely recommended by Brazilian health authorities to the management of DENV infection. Consequently, they are not available in the primary care services where patients with DENV are seen. Therefore, our study reinforces the view that at least a routine 12-lead ECG be taken from every patient with DENV. In this regard, it is important to emphasize that the take of the 12- lead ECG is inexpensive, easy to perform, highly indicative of subtle cardiac disease, and noninvasive. Patients with ECG abnormalities should undergo transthoracic echocardiogram as well as troponin serum levels measure to detect heart involvement in DENV [20].

Another potential explanation for our findings is the occurrence of electrolyte disturbances, which have been found in DENV, but with no association with ventricular repolarization alterations. We did not measure electrolytes in view of lack of facilities where the patients were seen. Because the lack of evidence between electrolyte alterations and ventricular repolarization changes in patients with DENV, we do not believe that electrolyte disturbances are the cause of the lengthening of the QTc interval detected in our investigation.

It is interesting to note that, despite changes in the QTc interval, patients with DENV did not show abnormalities in the QT interval dispersion. QT interval dispersion is a marker of inhomogeneous myocardial repolarization associated with regional electric abnormalities or patch fibrosis [14,24-25]. Therefore, the lack of abnormalities in the QT interval dispersion suggests that, in patients with DENV, the myocardial disease process is acute, not depending on fibrosis, as has been observed in fibrosing cardiomyopathy [14].

Our study has limitations. The small sample size precludes a firm conclusion about the data obtained. Electrolytes (K^+, Mg, Ca^{++}) were not measured in view

of the poor facilities where the patients were seen. Only patients with non- complicated DENV were evaluated; therefore, our results cannot be extrapolated to patients with complicated DENV. Finally, we did not follow up these patients; therefore, we cannot know if such ECG abnormalities disappeared with time, as observed in a patient with Takotsubo cardiomyopathy secondary to DENV [13].

However, it must be emphasized that our study was performed during an epidemic, in the primary care setting where the majority of patients with DENV are seen in underdeveloped countries, and referral to tertiary centers sounds like a premium because the massive number of patients observed during DENV outbreak. The access to standard laboratory tests and 12 lead ECG and echocardiogram is not usually available in this scenario. In the literature, many reports of cardiac alterations in patients with severe dengue are described. Our work adds to the medical knowledge on this disease by identifying cardiological alterations in patients with non-severe dengue as well.

The routine 12-lead ECG is not recommended by local authorities. Our work points out that a significant proportion of patients with DENV will show abnormalities in ventricular repolarization. This means that they can be regarded as a marker of myocardial involvement even though the rest of the 12-lead ECG is normal, and that patients portend this abnormality should be followed up closely in view of the potential clinical consequences of such a disorder.

Conclusion

Our study shows that myocardial repolarization changes do occur in patients with DENV. Having into account the potential impact of these changes on patients' outcome, we do recommend a 12-lead ECG for each patient with DENV.

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