

Dengue with Bradycardia: Clinical Predictors and Prognostic Significance

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Abstract: *The severity of dengue ranges from mild illness to Dengue haemorrhagic fever (DHF) & dengue shock syndrome (DSS). Early assessment of severity & appropriate management is essential in reducing mortality. The severity of dengue is assessed by narrow pulse pressure, thrombocytopenia & haemoconcentration. Relative & absolute bradycardias have been reported in dengue. Our study aims to find the demographic & clinical features which correlate with bradycardia in dengue & whether bradycardia is a marker of disease severity.*

Keywords: dengue bradycardia dss relative bradycardia

1. Introduction

The severity of dengue ranges from mild illness to Dengue haemorrhagic fever (DHF) & dengue shock syndrome (DSS). Early assessment of severity & appropriate management is essential in reducing mortality. The severity of dengue is assessed by narrow pulse pressure, thrombocytopenia & haemoconcentration. Relative & absolute bradycardia has been reported in dengue. Our study aims to find the demographic & clinical features which correlate with bradycardia in dengue & whether bradycardia is a marker of disease severity.

2. Objective

To find demographic & clinical predictors of bradycardia in dengue.

3. Methods and materials

Study design: Longitudinal study

Study duration: 12 months

Study population: Patients admitted in Father Muller Medical College with diagnosis of Dengue fever by NS1 antigen method with an ECG revealing sinus bradycardia (with no evidence of heart block) or no history of cardiac disease in the past. Patients with relative bradycardia were not included in this study.

Sample size: $N = \frac{(Z_{\alpha/2})^2 pq}{D^2}$

P = prevalence of dengue fever in south India (32 per million population)(1)

Q=1-p

$\alpha=0.05(1.96)$

D=Relative precision (20% of p)

N=125

Analysis of data will be done with chi square test and ANOVA test

Inclusion criteria:

- 1) Age 18yrs-70yrs
- 2) Bradycardia

Exclusion criteria:

- 1) Dengue shock syndrome
- 2) Previous cardiovascular events
- 3) Beta blocker use

4. Review of Literature

A study published in JAPI in 2014 revealed 8 out of 48 patients with dengue had sinus bradycardia.⁽²⁾

Another study showed that mean heart rates were lower in dengue, the average pulse rate 87.6 beats/min with mean temperature being 104.6 (p<0.0001).⁽³⁾

A study done in south India showed more than 80% of the cases had bradycardia. Among them 60% percent had relative bradycardia.

4.1 Spectrum of involvement

Dengue virus infection affects the heart structurally and functionally. Clinical manifestations of cardiac complications secondary to dengue virus infection vary from self-limiting arrhythmias to severe myocardial infarction, leading to hypotension, pulmonary oedema, and cardiogenic shock.⁽⁴⁾

Most of the dengue virus infections are symptomatic and can present with a wide range of clinical manifestations, from mild febrile illness to life-threatening dengue shock syndrome.

Aside from systemic manifestations, variable cardiac complications can also be seen in dengue fever. Most cases of dengue have an asymptomatic myocardial involvement with ECG changes including T inversions and ST-T changes.⁽⁵⁾

Other presentations can include bradycardia⁽³⁾, atrial fibrillation⁽⁶⁾, second degree heart block (mobitz type 1)(7), and ventricular arrhythmia⁽⁸⁾

Cases of acute pulmonary oedema and cardiogenic shock associated with left ventricular failure.⁽⁹⁾ have been reported with severe myocardial cell damage

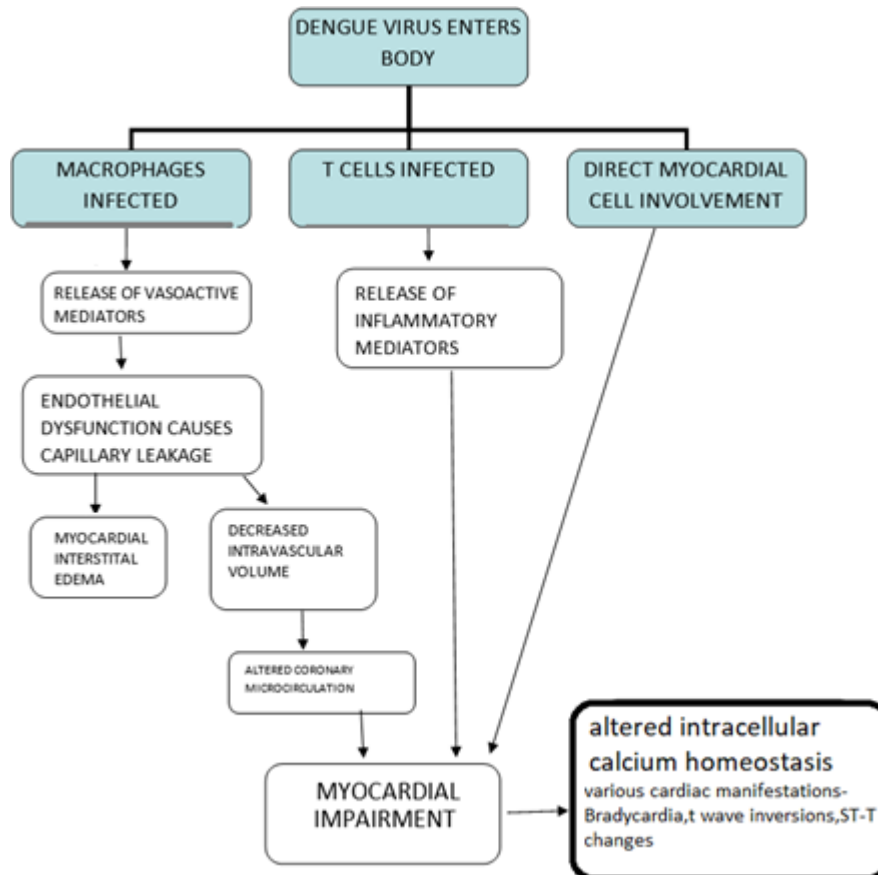


Figure 1: Pathophysiology of ECG changes and bradycardia in Dengue fever

Pathophysiology in a study done in Sri Lanka revealed that cardiac involvement in Dengue has been closely associated with DENV-2 and DENV-3 serotypes.⁽⁵⁾

A report from Sri Lanka showed that 62.5% of 120 adults with dengue fever had ECG abnormalities.⁽⁹⁾ It was also noted that cardiovascular complications of DF are under-diagnosed because they are mild and reversible in most of the cases without the need for further intervention.⁽⁹⁾

Bradycardia is commonly observed in the convalescence phase due to predominant parasympathetic activity. It can potentially proceed to other arrhythmias including complete heart block.⁽¹⁰⁾

Bradycardia was a predominant occurrence amongst total of 100 cases of Dengue fever analysed. 88% of the cases had bradycardia. (61% had relative bradycardia and 27% bradycardia. Majority of the patients on ECG showed sinus bradycardia (37%) and normal sinus rhythm (48%). Hence, awareness of bradycardia as a clinical finding, can help in the early recognition of Dengue and potentially reduce complications and death associated with dengue virus infection.⁽¹¹⁾

A study based on Heart rate variability showed that cardiac parasympathetic activity is responsible for the majority of the HR reduction following defervescence in patients with dengue viral infection.⁽¹²⁾

La-Orkhun et al. assessed HRV as an index of autonomic function in patients with DF, and found no significant changes in various time and frequency domain metrics of HRV at least 24 h after defervescence and follow-up conducted at least 14 days after defervescence. Since monitoring was performed 2 weeks after hospital discharge, it is unlikely that changes in HRV during the critical phase of illness would have been detected in their study.⁽¹⁰⁾

Dengue fever may adversely affect cardiac function. An echocardiographic study by Khongphattha-nayothin et al. showed decreased myocardial contractility and suboptimal heart rate response in some patients with DHF⁽¹³⁾. The exact mechanism of the cardiac injury in dengue fever remains unknown, however it is proposed that the direct invasion of the cardiac myocyte by the virus and damage to the cardiac cells by the ongoing inflammatory damage are the major mechanism of the cardiac manifestations. Dengue virus upon its entry in the body is taken up by the macrophages which cause activation of the T cells. These activated T cells cause release of various inflammatory cytokines, interleukins (IL1, IL2, IL6 etc), tumour necrosis factors (and activation of the complement pathway (C3a, C5a) and histamine⁽¹⁴⁾. In another study also it was noticed that the concentrations of cytokines, including tumour necrosis factor, interferon- γ , interleukin-8 (IL-8), IL-10, and IL-12, are substantially increased during dengue infection. Their levels likely correlate with specific clinical manifestations and illness severity.⁽¹⁵⁾

Acute reversible hypokinesia (reduction in left ventricular ejection fraction) was also reported by Wali et al.⁽¹⁶⁾. The underlying mechanisms were postulated to be immune in origin, although myocarditis was also postulated as a contributory factor. Fever production in response to exogenous pyrogens is believed to be mediated mostly by cytokine prostaglandin pathways, and neural input is important in the early phases of fever.⁽¹⁷⁾

5. Results

5.1 Gender distribution

In the study majority of the subjects were males with 66.4% of the total subjects (125) being males.

Table 1: Gender Distribution

	Frequency	Percent
Female	42	33.6
Male	83	66.4
Total	125	100.0

Occupation

Majority of the subjects were heavy workers making up around 67.2% of the cases of dengue with bradycardia.

Table 2: Occupation

Occupation	Frequency	Percent
Sedentary worker	13	10.4
Moderate worker	28	22.4
Heavy worker	84	67.2
Total	125	100.0

Age Group

Patient selected were predominantly in the middle age group.

Table 3: Age distribution

Age group	Frequency	Percent
<20 years	1	0.8
21-30 years	46	36.8
31-40 years	31	24.8
41-50 years	47	37.6
>50 years	0	0
Total	125	100.0

Bleeding manifestations

Only 3% of the total subjects had any bleeding manifestations.

Table 4: Bleeding manifestations

Bleeding manifestations	Frequency	Percent
Absent	122	97.6
present	3	2.4
Total	125	100.0

Rashes

73% had rashes during the course of disease.

Table 5: Rashes

RASHES	Frequency	Percent
Absent	52	41.6
Present	73	58.4
Total	125	100.0

Respiratory complications

Only 11.2% of the total cases had respiratory complications.

Table 6: Respiratory complications

Respiratory complications	Frequency	Percent
nil	111	88.8
yes	14	11.2
Total	125	100.0

Pulse pressure(less than 40)

In this study 55 cases had low pulse pressure. At the time of presentation. Pulse pressure of less than 40 mmHg was defined as abnormal in the study

Table 7: Pulse Pressure

Pulse pressure	Frequency	Percent
normal	55	44.0
abnormal	70	56.0
Total	125	100.0

Liver Enzymes-AST/ALT(more than 50)

Patients were found to have elevated AST and ALT (70.4% and 62.4% respectively) at the time of presentation.

Table 8: Liver Enzymes-AST/ALT (more than 50)

AST	Frequency	Percent
Valid normal	37	29.6
Valid abnormal	88	70.4
Total	125	100.0

ALT	Frequency	Percent
Valid normal	47	37.6
Valid abnormal	78	62.4
Total	125	100.0

BILIRUBIN

Only 9.6% had elevated bilirubin

Table 9: BILIRUBIN

BILIRUBIN	Frequency	Percent
normal	113	90.4
abnormal	12	9.6
Total	125	100.0

PCV On day of presentation

PCV was found to be abnormal in 29.6% at the time of presentation and 34.4% had elevated PCV on the day of presentation.

Table 10: Comparing PCV On day of presentation and PCV on day of bradycardia

PCV On day of presentation	Frequency	Percent
normal	88	70.4
abnormal	37	29.6
Total	125	100.0

PCV on day of bradycardia	Frequency	Percent
normal	82	65.6
abnormal	43	34.4
Total	125	100.0

Platelet on the day of presentation

It was seen that 26% of the patients had very low platelets of less than 50000/ml at the time of presentation. But only 4.8% cases and had platelets of less than 50000/ml. It was noticed that only a very few cases had significantly low platelets on the day of bradycardia.

Table 11: Comparing Platelet on the day of presentation vs Platelets on day of bradycardia

PLATELET on the day of presentation Platelets in lakhs	Frequency	Percent
<0.20	10	8.0
0.21-0.50	23	18.4
0.51-1.00	50	40.0
1.01-1.50	31	24.8
1.51-4.50	11	8.8
Total	125	100.0

Platelets on day of bradycardia Platelets in lakhs	Frequency	Percent
<0.20	1	0.8
0.21-0.50	5	4
0.51-1.00	40	32
1.01-1.50	59	47.2
1.51-4.50	17	13.6
>4.51	3	2.4
Total	125	100

Clinical phase during which patients with bradycardia presented

Majority of the patients with sinus bradycardia presented during the febrile phase of illness and bradycardia was observed predominantly in the recovery phase of the illness.

Table 12: Clinical phase during which patients with bradycardia presented vs the day when bradycardia developed

Clinical phase during which patients with bradycardia presented	Frequency	Percent
Febrile phase	85	68%
Critical phase	36	28.8%
Recovery phase	4	3.2%
Total	125	100.0%

Clinical phase during which Bradycardia developed	Frequency	Percent
Febrile phase	11	8.8%
Critical phase	10	8.0%
Recovery phase	104	83.2%
Total	125	100.0%

Table 13: Clinical spectrum

Clinical spectrum	Frequency	Percent
Dengue fever	120	96.0%
DHF	4	3.2%
DSS	1	0.8%
Total	125	100.0%

Of the total 125 patient admitted with sinus bradycardia only 1 patient developed DSS and 4 patients had DHF. There was no mortality observed in any patients during this study

6. Discussion

In this study which included 125 patients dengue patients presenting with sinus bradycardia 66.4% were males and most of the patients belonged to heavy manual labour group. Only 2.4% of the patients had bleeding manifestations.

73% of the total patients had maculopapular rashes on the body. 11.2% of the total patient developed respiratory complications.

56% of the patients with bradycardia had pulse pressure of less than 40 at the time of presentation. During presentation an elevated bilirubin was seen only in 9.6% and raised AST & ALT enzymes (more than 50) was seen in 70.4 and 62.4% patients respectively. It was seen that PCV on the day of presentation s normal in 70.4 of the patients and on day of bradycardia was normal in 65.6 and abnormal in 34.4 showing no major differences in PCV.

It was seen that 26% of the patients had very low platelets of less than 50000/ml at the time of presentation. But only 4.8% cases and had platelets of less than 50000/ml. It was noticed that only a very few cases had significantly low platelets on the day of bradycardia.

Majority of the patients presented during the febrile phase of illness and 28.8% during critical part of illness. It was seen that bradycardia was seen predominantly in the recovery phase of illness 104(83.2%). This was consistent with another study by La-Orkhun et al and had suggested the cardiac parasympathetic activity during recovery phase to be responsible for bradycardia.⁽¹⁰⁾

Another study done in India showed Dengue fever associated with high prevalence of bradycardia (relative and sinus bradycardia) and was seen predominantly in recovery phase of the illness.⁽¹¹⁾

Of all the patients admitted with sinus bradycardia only 1 patient developed DSS and 4 patients had DHF. There was no mortality observed in any patients during this study

7. Conclusion

- Dengue fever was associated with bradycardia predominantly in the recovery phase of illness.
- Majority of the patients with sinus bradycardia were seen in heavy labour group.
- Most of the patients that developed bradycardia during the course of stay in hospital were noticed to have low PCV at the time of presentation.
- Sinus bradycardia was not associated with significant complications and did not correlate with disease severity. Of the 125 subjects only 1 patient developing DSS and 4 patients developing DHF.

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