Original Research Article

Effect of co morbidities on the clinical outcome of Dengue fever

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ABSTRACT

Background: Dengue is the most rapidly spreading mosquito-borne viral disease in the world. A number of Dengue Haemorrhagic Fever (DHF) risk factors had been suggested. However, these risk factors may not be generalized to all populations and epidemics for screening and clinical management of patients at risk of developing DHF/ Dengue shock syndrome (DSS).
Methods: A hospital based prospective case control study was done by taking 40 cases each of dengue fever with diabetes mellitus, hypertension, diabetes and hypertension and 30 cases of dengue with asthma/COPD and these patients were compared with controls of 100 patients with dengue fever but no comorbidities. All patients had Dengue serology NS1 or IgM positive.
Results: Patients admitted with dengue fever with comorbidities had increased duration of hospitalization with P value of 0.012. The clinical outcome of the 250 patients. In the subgroup of dengue fever patients with DM and Dengue fever with DM and HTN, they were noted to have a 2.69 and 3.06 times increased risk effect of DHF.
Conclusions: Dengue fever with DM or DM with HTN have a higher risk of developing DHF when compared with patients with dengue fever with no comorbidities. This finding helps us in triaging patients with comorbidities who develop dengue fever for specialized care and closer clinical monitoring.

Keywords: Comorbidities, Dengue fever, Dengue haemorrhagic fever, Diabetes mellitus, Dengue shock syndrome, Hypertension

INTRODUCTION

Dengue fever is an acute febrile disease characterized by sudden onset of fever for 3 to 5 days, intense headache, myalgia, retro-orbital pain, anorexia, gastrointestinal; disturbances and rash.[1]

Dengue is now endemic in most tropical countries, subtropical countries.[2] DHF is characterized by increased vascular permeability, hypovolemia and abnormal blood clotting mechanisms.

Dengue fever (DF) with its severe manifestations such as DHF and DSS has emerged as a major public health problem of international concern. The geographical distribution has greatly expanded over the last 30 years, because of increased potential for breeding of Aedes aegypti. This has been prompted by demographic explosion, rapid growth of urban centers with strain on public services, such as potable water and augmented by rain water harvesting in diverse types of containers resulting in multiple storage practices.[3]

Today dengue ranks as the most important mosquito-borne viral disease in the 0world. Current estimates report that, at least 112 countries are endemic for Dengue and about 40% of the world populations (2.5-3 billion people) are at risk in tropics and subtropics.[4] Annually 100 million cases of dengue fever and half a million cases of DHF occur worldwide.[5] Very few diseases in India cause the degree of consternation, concern and political upheaval as that of dengue.[6-8]

The mean age of acute dengue has undergone a shift towards older ages. This fact points towards the relevance of assessing the influence of age-related comorbidities, such as diabetes, on the clinical presentation of dengue episodes. Identification of factors associated with a severe presentation is of high relevance, because timely treatment is the most important intervention to avert complications and death.[9]

METHODS

A hospital-based case control study was carried out over a period of 2 years from November 2012-October 2014. 250 Patients aged more than 18 years or older identified as probable cases by clinical suspicion, admitted to KIMS Hospital, Bengaluru, were registered in the study. The case definition was based on the compatible history and examination, confirmed by Dengue serology as either NS1 or IgM positive. Patients with an initial platelet count of less than 100,000 were included in the study. Patients with an identified specific infection such as malaria, scrub typhus, enteric fever, leptospirosis were excluded from the study.

The data was collected by using a predesigned and a pretested questionnaire which included the following details like a detailed demographic data, clinical history, physical examination. Relevant baseline investigations were undertaken. For all the subjects the Dengue rapid test was done. During the study, based on the above criteria, serum samples were obtained on an average on 4 days after dengue symptoms had appeared.

The number of patients included was 250. Of which they were divided into 100 controls of patients with dengue fever and 40 patients Dengue fever with diabetes mellitus, 40 of dengue with hypertension, 40 of dengue with diabetes and hypertension and 30 patients of dengue with asthma selected by purposive sampling. The cases were followed up daily for the clinical and laboratory parameters. The patients were treated with analgesics, IV fluids and as per the requirements for complications.[10,11] The patients were stratified based on the presence or absence of complications. The frequency of various signs and symptoms and the values of various laboratory tests were compared.

The other investigations done for the purpose of the study were complete hemogram, blood urea and serum creatinine, random blood sugars, urine routine, ECG, liver function test, dengue serology- NS1 Ag and IgM and IgG, Leptospira IgM and IgG, QBC for Malarial parasite, Widal test, Chest X-Ray and Ultrasound abdomen and pelvis for supportive evidence. Special investigations to be done if required were HbA1C and 2D-ECHO. The investigations were repeated as and when necessary.

The data was entered in Microsoft Excel 2013. Data was analyzed in Statistical Package for Social Sciences version 21.0. Results were expressed in proportions and percentages with appropriate charts, tables and graphs. Chi-square test was applied to find out the level of association between two proportions. If the 'p' value obtained from chi Square test is less than 0.05, then it is considered statistically significant. Institute Ethical committee approval was obtained before starting the study. Informed written consent was obtained from all the study subjects. The study subjects were treated as per the WHO protocol.[10]

RESULTS

The patients in this study were age matched with age group of each subgroup i.e. in controls they were 45.06 years, in Diabetes mellitus group they were 45.85 years, in Hypertension group they were 47.73 years, in DM and Hypertension patients group they were 47.25 years and in Asthma subjects they were 41.13 years (Table 1).

Table 1: Comparison of age and sex distribution between the cases and controls.

Exposure	Cases		Controls	
	N	%	N	%
Age (years)				
DM - Mean (SD)	45.85		45.06	
HTN - Mean (SD)	47.73		45.06	
DM ĉ HTN - Mean (SD)	47.25		45.06	
Asthma - Mean (SD)	41.13		45.06	
Sex				
Male	64	42.7%	42	42.0%
Female	86	57.3%	58	58.0%

In the present study, of the total 150 cases 42.7% were males and 57.3% were females. In the control group of 100 patients, 42% were males and 58% were females. This showed that this study is done a sex matched distribution as well (Table 1).

Random blood sugar was increased in 38.7% of cases as against 13% percent increase in RBS noted in the control group. This difference was statistically significant with a P value of 0.001.

The mean duration of hospitalization was 6.39 days in the control group, 6.83 days in the DM group, 6.35 days in the HTN group, 7.78 days in the DM and HTN group, and 5.77 days in the asthma/COPD group. While taking an arbitrary division of duration of hospitalization to be less than 7days and more than 7 days, it was found that the duration of hospitalization was found to be longer for the cases group with comorbidities as compared to the controls with the P value of 0.012 being statistically significant.

In the DM group of cases, of the total 40 patients, 30 (75.0%), 8 (20.0%), 1 (2.5%), and 1 (2.5%) had classical dengue fever, DHF, DSS and Death respectively. In the HTN subgroup of cases all 40 (100.0%) patients had classical dengue fever. In the DM and HTN subgroup, of the total 40 patients, 29 (72.5%) of patients had classical dengue fever, there was one death (2.5%) and 10 (25.0%) patients had DHF. In the asthma/COPD group of the total 30 patients, 29 (96.33%) of patients had classical dengue fever and one patient had DHF. In the control group of 100 patients, 89% had classical dengue fever, 10% had DHF, 1% had DSS and no deaths were noted (Table 2).

Table 2: Distribution of clinical outcome between cases groups and controls.

Outcome	DM n (%)	HTN n (%)	DM ĉ HTN n (%)	Asthma/COPD n (%)	Controls n (%)	Total n (%)
DF	30 (75.0)	40 (100.0)	29 (72.5)	29 (96.33)	89 (89.0)	217 (86.9)
DHF	8 (20.0)	0 (0.0)	10 (25.0)	1 (3.33)	10 (10.0)	29 (11.6)
DSS	1 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	2 (0.8)
Death	1 (2.5)	0 (0.0)	1 (2.5)	0 (0.0)	0 (0.0)	1 (0.8)
Total	40 (100.0)	40 (100.0)	40 (100.0)	40 (100.0)	100 (100.0)	250 (100.0)

Since the outcome in terms of DSS and Death were fewer in number statistical analysis cannot be computed for the outcome. Hence statistical analysis was done to find out the risk association only for DHF (by also including the outcome death and DSS under DHF) with co-morbidities.

In the DM group the outcome of DHF was statistically significant compared to age and sex matched control group with a P value of 0.04 and an Odds ratio of 2.69 (95% CI 1.04-6.98) indicating that patients with DM had 2.69 times more risk of developing DHF which was also

statistically significant. There was no significant difference in the outcome of statistical significance in this group of hypertensive patients as compared to controls. In the DM and HTN group the outcome of DHF was statistically significant compared to age and sex matched control group with a P value of 0.02 and an Odds ratio of 3.06 (95% CI 1.20-7.81) indicating that patients with DM had 3.06 times more risk of developing DHF which was also statistically significant. There was no significant difference in the outcome of statistical significance in this group of Asthma/COPD patients as compared to controls (Table 3).

Table 3: Comparison of clinical outcome between controls and various risk group.

	Cases (n=40)	Controls (n=100)	P value	OR	95% CI
DHF with DM	10 (%)	11(%)	0.04	2.69	1.04-6.98
DHF with HTN	0	11	0.10		
DHF with DM and HTN	11	11	0.02	3.06	1.20 - 7.81
DHM with asthma/COPD	1	11	0.21	0.28	0.03-2.25

DISCUSSION

With regards to the duration of hospitalisation it was found to be longer for the cases group as compared to the controls with the P value of 0.012 in this study. This was similar to the finding in the study by Pang et al which reported that the median length of hospitalization was five days (IQR: 4-7 days) longer in patients with

comorbidities than dengue patients without comorbidities.[12]

To our knowledge this is the first study to find evidence of increased levels of hyperglycaemia in patients with comorbidities compared to those without any comorbidities.

In the study done by Aggarwal et al, diabetes (OR: 2.12; 95% CI:1.34-4.65) (<0.0001) was associated with severe Dengue.[13,14] Lee et al, found that DM2 was an independent risk factor for DSS (adjusted odds ratio [AOR]=7.473; 95% confidence interval [CI]=2.221-25.146) and SD (AOR=6.207; 95% CI=2.464-15.636) DM2 patients with additional comorbidities and DM2 patients with suboptimal glycaemic control irrespective of comorbidities were significantly at higher risk for the development of DHF/DSS/severe dengue.[15] In the study by Werneck et al, done in Brazil, the risk of dying was significantly increased with the combination of severe dengue haemorrhagic fever and underlying comorbidities (CFR 15.33%, RMR 106, 95% CI 71-159, p<0.001) compared to individuals with dengue alone (non-severe dengue and no underlying comorbidity). Furthermore, there was a 1.7-fold higher prevalence of severe dengue associated with comorbidities (8.4%, p<0.001), compared to without comorbidities (4.8%).[16] The study by Chen et al, concluded that dengue patients with diabetes tended to have more severe thrombocytopenia and were more likely to have DHF/DSS.[17] Pang et al, found that ICU patients with severe Dengue were more likely to be diabetic(p=0.031)and similar findings are noted in other studies.[18-21] Few studies have found a negative correlation with comorbidities leading on to Dengue haemorrhagic fever.[22]

In the study done by Pang J et al, for co-morbidities, diabetes mellitus remained an independent risk factor for DHF outcome (AOR=1.78; 95% CI:1.06-2.97) in year 2007 and 2008. They investigated the risk effect of DHF outcome on patients having diabetes mellitus with hypertension, hyperlipidaemia or asthma. Only diabetes mellitus with hypertension (AOR=2.43; 95% CI:1.42-4.15) were observed to be significantly associated with DHF outcome.[23]

In this study, similar findings were noted in that, diabetes mellitus patients (OR=2.69 95% CI:1.04-6.98) and diabetes with hypertension patients (OR = 3.06 95% CI: 1.20-7.81) had a higher risk effect of DHF outcome. Similar to the above study no risk effect was found between outcome of DHF in patients with hypertension alone or asthma/COPD alone

Pathogenesis for the poorer outcomes for patients with diabetes can be attributed to aberrant immune over-activation with cytokine overproduction in dengue patients leading to the development of a great array of manifestations.[24-26] Some of the activated cytokines are pro-inflammatory, while others are anti-inflammatory, and together they cause leukocytes to activate synergistically or antagonistically.[27] Clinical, histopathological and laboratory manifestations in dengue-affected patients are the net effect of the interactions between one another among these activated cytokines.[26,27] Poor outcome for hypertensive individuals can be due to elevated C-reactive protein levels in the blood, which increases capillary permeability and risk of

coagulopathy.[28,29] Remarkably, increased vascular permeability leading to plasma leak is unique in DHF/DSS/severe dengue.[30,31]

There were a few limitations in this study, first of it being the study was carried out in a single centre so the results may not be exactly replicated in studies done at a multicentre level because of wide demographic variations within India. Secondly, we did not have the data sub stratified according to whether the findings are varying in primary and secondary dengue. Further studies are required with larger sample size of patients with comorbidities to be compared with patients having no comorbidities.

CONCLUSION

Hyperglycemia was noted in patients which required management with adequate clinical monitoring. Further studies need to be done to find out the extent of development of hyperglycemia in previously normoglycemic patients. The duration of hospitalization is higher for patients with comorbidities compared to the patients with no comorbidities.

Patients with comorbidities such as Diabetes mellitus or Diabetes mellitus with Hypertension having dengue fever have a higher risk association with the outcome of Dengue haemorrhagic fever compared to an age and sex matched controls with no comorbidities. This finding helps us in triaging patients with comorbidities who develop dengue fever for specialized care and closer clinical monitoring.

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