Association of metabolic factors with dengue viral infection on admission triage which predict its clinical course during Lahore dengue epidemic

Amena Moazzam Baig Mirza,[1] Madiha Fida,[2] Ghulam Murtaza,[3] Rizwan Niazi,[4] Asif Hanif,[5] Khadija Irfan,[6] Faisal Masud[7]

Abstract

Objective: The study was done to identify metabolic factors which were associated with an increased risk of dengue haemorrhagic fever in clinically diagnosed patients of dengue viral infection.

Methods: 563 patients with dengue viral infection that presented to 3 tertiary care hospitals of Lahore were included in this study, out of which approximately half of the patients were diagnosed as dengue haemorrhagic fever.

Results: A total of 563 patients with 263(46.7%) dengue fever and 300(53.3%) dengue haemorrhagic fever patients were studied. The mean age of patients was 48.48 ± 20.07 years. In patients younger than 60 (n=355), 171 patients had DF and 184 had DHF, while 116 patients above 60 years had DHF and 92 had DF (n=208). The presence of metabolic risk factors such as diabetes (OR = 2.146), hypertension (OR =1.65), diabetes and hypertension (OR =3.56), abnormal liver function tests (OR = 2.27), abnormal renal function tests (OR = 2.282) all increased the risk of DHF relative to DF.

Conclusion: The study showed that metabolic factors especially diabetes with and without hypertension are important risk factors for the development of DHF.

Keywords: DHF: Dengue hemorrhagic Fever, DF: Dengue Fever, LFT: Liver Function tests, RFT: Renal Function Test.
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Introduction

Dengue fever is a mosquito borne viral infection, which is endemic in over 100 tropical and sub-tropical countries worldwide. According to WHO, two fifth of the world population is now at risk of dengue fever. An approximate number of 30 million new cases of dengue fever occur annually worldwide and 500,000 cases of DHF requiring hospitalization with a mortality rate of 2.5%.[1] Patients infected by dengue virus are either asymptomatic in majority of cases or may produce a wide clinical spectrum ranging from mild flu like disease (dengue fever with and without haemorrhages) to severe form (dengue haemorrhagic fever) characterized by coagulopathy, vascular wall fragility and its increased permeability. The latter condition is associated with shock and ultimately death[2,3] while the former follows a benign course requiring only supportive care.

The exact pathogenesis of development of DHF/DSS is still not fully understood despite extensive studies. Various theories have been put forward including virulence dengue virus subtype-2 (DEV 2) prone to DHF as compared to DF), activation of immune complex,

enhanced antibody response, compliment activation and release of cytokines which disrupt the integrity and increase vascular permeability.[4-8] It has been postulated that certain co morbid conditions like diabetes mellitus, hypertension and chronic renal failure predispose patients more to develop dengue haemorrhagic fever. The activated immune response and enhanced cytokine release is responsible for the endothelial dysfunction seen in type 2 diabetics.[9-11] This disruption of endothelium integrity and its dysfunction, a hall mark of pathogenesis of dengue haemorrhagic fever, is thought to be enhanced in pro inflammatory states like diabetes mellitus. It is also seen that patients with diabetes and hypertension are more prone to DHF than those without hypertension, further implicating endothelium dysfunction as a causative factor.[12] Diabetes mellitus and hypertension both are an important component of metabolic syndrome, a syndrome highly prevalent in South Asia.[13-15] The increased chance of encountering these two conditions together advocates the need to study them as risk factors for development of DHF/DSS. Certain epidemiological studies have focused on the patient factors in the past and have shown that females, children below 15 years and those above the age of 65 years were shown to be more prone to DHF.[12] No definite therapeutic agent for DHF/DSS is available till date, thus early clinical recognition and anticipatory treatment of those at risk of DHF/DSS can save their lives.[2]

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[1]Department of Endocrinology and Metabolism, Services Hospital, [2]House Officer, [3,4]Medical Officer, [6,7]Department of Endocrinology and Metabolism, Services Hospital, [5]Department of Biostatistics, Ghulab Devi Hospital, Lahore.
Correspondence: Amena Moazzam Baig Mirza. Email: amenamb14@gmail.com

The first outbreak of Dengue infection in Pakistan was reported in 1994 and its prevalence has been on the rise ever since.[16] In Lahore Dengue Epidemic 2011, a total of 590339 suspected cases of dengue were reported, out of which 21685 were confirmed serologically. According to an estimate 5-10% cases developed DHF and <5% went to DSS, with a mortality rate of less than 1% (Punjab Health Department).[17]

The current study was designed to identify those metabolic factors on admission triage which predispose to a more aggressive course of dengue infection (leading to DHF/DSS). Knowledge of these factors will enable the clinicians on triage to identify those patients likely to follow a critical path and help in their timely admission and management at higher level of care.

Methods

Study Design: A cross sectional study was conducted during the Lahore Dengue Epidemic 2011. Data was collected from three tertiary care centers of Lahore namely Mayo hospital, Sir Ganga Ram hospital and Services Hospital. The duration of sample collection was 4 weeks from 10-10-2011 to 10-11-2011

Sample Size: Non-probability convenient sampling was done and the admission record of total of 563 patients was collected in which there was 300 cases of DHF and while the remaining had dengue fever.

Inclusion Criteria

A. Patients with dengue viral infection were included in this study, the cases were defined according to the revised WHO 2009 criteria.

Case definition of Dengue viral Infection

◆ Probable dengue patients with and without warning signs: who live in/ travel to dengue endemic areas. Fever and 2 of following criteria: nausea, vomiting, positive tourniquet sign, leukopenia, and any warning sign (abdominal tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleed, lethargy, liver enlargement >2cm, laboratory tests: increase HCT with rapidly decrease in platelets.

◆ Patients with severe dengue: Severe plasma leakage leading to shock, fluid accumulation with respiratory distress. Severe bleeding as evaluated by clinician .Severe organ involvement :Liver AST or ALT >1000,CNS :impaired consciousness, Heart and other organs

Metabolic factors that were studied were

Diabetes mellitus: Fasting blood sugar >126 mg/l, HbA1C >6.5% or history of known diabetic on medication.

Hypertension: systolic Blood pressure > 140mm Hg, diastolic >90mmHg or already on antihypertensive medication.

Chronic renal failure: persistently raised creatinine >2 for more than 3 months

Cardiovascular disease: acute coronary syndrome for duration less than 6 months.

Exclusion Criteria

All other cause of fever were ruled out on the basis of proper history and related tests.

Data Collection Procedure

Admission records of clinically diagnosed cases of Dengue infection were studied with prior consent from Head of Department of the concerned wards. Dengue infection was diagnosed according to Case Definition described by WHO guidelines.[18] Data regarding demographics, related complications and co morbid metabolic diseases was collected. Ethical approval for this study was taken by Institutional Review Board, Services Hospital Lahore. All information was collected by researcher and kept in self designed proforma.

Data Analysis

All the collected data was entered and analyzed using SPSS version 20. Quantitative variables like age of patients were presented in form of mean ± S.D. Qualitative data like gender, type of dengue infection (DF or DHF) and metabolic factors such as (diabetes, hypertension, etc.) were presented as frequencies and percentages. Odds ratio was used to measure the risk of DHF in presence of difference metabolic conditions and Chi-square test was applied to measure the association between DF/DHF and co morbid conditions. P-value ?0.05 was considered as significant.

Result

Demographic Data: A total of 563 cases studied of which 300(53.3%) dengue hemorrhagic fever and 263(46.7%) dengue fever patients were studied. The mean age of patients was 48.48 ± 20.07 years. In patients younger than 60 (n=355), 171 patients had DF and 184 had DHF, while 116 patients above 60 years had DHF and 92 had DF (n=208). There was an overall female predominance with 348(61.8%) patients with a male to female ratio of 1:1.62. Using Chi-square test we found no association between age groups and the occurrence of DHF vs DF. Among 215 male patients 99 had DF and 116 had DHF while in 348 female patients DF (n=64) and DHF (n=184 patients). However the gender difference in the occurrence of DHF vs DF was not statistically significant. (P-value = 0.803) as

Table-1: Demographic results of dengue infected patients.

Demographics	Dengue Fever (n)	Dengue Haemorrhagic Fever(n)	P value
Age			
<60 years	171	184	0.366
>60 years	92	116	
Gender			
Male n=215	99	116	0.803
Female n=348	64	184	

Table-2: Frequency of metabolic factors/co morbid conditions among dengue infected patients.

Risk Factors	Number of Patients (n)	Frequency (%)
Diabetes mellitus	246 patients	44 %
Hypertension	137 patients	24 %
Diabetes mellitus and hypertension	60 patients	11%
Impaired liver function tests	27 patients	5 %
Impaired Renal function tests	29 patients	5 %
Myocardial infarction	32 patients	5.8%
Stroke	30 patients	5.3%

shown in Table-1.

Metabolic Fisk Factors: The overall prevalence of different metabolic risk factors determined in the patients with Dengue infection are shown in Table-2.

Co-Morbid Conditions: Co morbid conditions like myocardial infarction and stroke were also studied. The results shown in Table-2.

Effect of metabolic risk factors and co-morbid conditions on the clinical course of DHF: The presence of metabolic risk factors and co morbidities at admission triage were corrected with clinical course of Dengue

infection for the development of DHF versus uncomplicated DF. The results are shown in the Table-3.

Discussion

The clinical spectrum of dengue infection varies from a benign course seen in dengue fever to a more severe and devastating course in dengue haemorrhagic fever. The key to their successful treatment is dependent on the early clinical recognition of type of dengue infection and anticipatory management of those who are more prone to develop DHF/DSS.[2,3] The identical initial clinical presentation of both DF and DHF and the short course of the disease make the timely identification of patients at risk of DHF a challenging task. This requires not only close monitoring of key clinical indicators but also recognition of certain metabolic factors like diabetes, which predicts a more aggressive clinical course. Diabetes mellitus, is characterized by production of pro inflammatory cytokines and endothelial dysfunction[9-11] which might have the potential to augment the cytokine storm seen in DHF.

The Lahore Dengue Epidemic 2011, is considered to be the largest epidemic of recent times.[19] This study was initiated keeping in view the possibility of identifying comorbidities which might predict the development of DHF in patients suffering from them. In our study, we found strong statistical association between certain metabolic factors and the development of DHF. Diabetes mellitus was found to be an independent risk factor for DHF (OR=2 .146, CI 1.52 - 3.013), and when combined with hypertension had a stronger association with DHF (OR 3.56; CI 1.96 - 6.49). Studies of dengue patients from other regions have reported a similar pattern of increased risk of DHF in the presence of comorbidities. In a Brazilian study done by Figueiredo et al diabetic patients had 2.75 (CI: 1.12-6.73) times the risk of developing DHF.[20] However, the association between DHF and patients suffering from hypertension by Figueiredo et al was much stronger (13

Table-3: Metabolic risk factors and presence of comorbidities at admission triage which predict the course of DHF versus DF (ODDs RATIO, 95%CI).

Risk factor		DHF	DF	χ^2	p-value	Odds ratio	95% C.I
Diabetes	Yes	141	105	19.73	< 0.001	2.146	1.52 - 3.013
	No	122	195				
Hypertension	Yes	77	60	6.55	0.010	1.65	1.23 - 2.441
	No	186	240				
Diabetes and Hypertension	Yes	44	16	19.11	< 0.001	3.56	1.96 - 6.49
	No	219	284				
	No	236	300				
	No	234	300				
	No	233	300				
Myocardial infarction	Yes	32	1	35.56	< 0.001	41.42	5.61 - 305.36
	No	231	299				

times) than that shown in our study (OR 1.65 CI: 1.23-2.441). A study from Singapore by Junxiong et al also reported a similar result, though the association between diabetic patients with and without hypertension (3.56 vs 2.16 and 2.1 vs 1.7) respectively during the Dengue epidemic of Singapore 2007-8[12] was not as significant as our results. Unlike the above mentioned two studies done in the past, our study also discussed other co morbid conditions like hepatic and renal diseases in reference to development of DHF. Among the Pakistani authors, Shahid et al, failed to show any statistical association between these co morbidities like diabetes with OR 1.26 (95% CI 0.78-2.03, p=0.34), hypertension OR 0.93 (95% CI: 0.57-1.49, p=0.76), and respiratory diseases like bronchial asthma (OR=1.34), pulmonary tuberculosis (OR=1.41) and DHF. However, the small size of the study may have led to this statistical insignificant result.[20]

Identification of metabolic risk factors for DHF can facilitate the clinician on triage of dengue patients at the time of admission, for proper assignment of level of care. This will help healthcare workers in third world dengue endemic areas to identify those at increased risk and make better use of limited health facilities available to them.

Our study had certain limitations .This was a retrospective study due to the sudden nature of the epidemic. Another limitation of the study was lack of serological confirmation of diagnosis in many patients. However, this accurately reflects the real time situation where due to the sudden and explosive nature of the epidemic.[21] Triage in this situation was done on the basis of clinical diagnosis recommended by WHO[18] and patients were managed accordingly. This study reported data as was actually recorded under those stressful circumstances. Another limitation might be selection bias as data was only collected of patients who reported and were admitted in the tertiary care units of Lahore city. In doing so we could have missed patients of dengue infection who might also have similar metabolic conditions like diabetes and were treated by general physicians but never reported to tertiary care hospitals, thus this data might only show tip of the ice berg. Lastly and most important, information about prior dengue infection which is thought to be the major risk factor to development of DHF[22,23] was not available due to limited health care resources in an epidemic state.

Conclusion

We concluded from the study that metabolic factors especially diabetes with and without hypertension, are important risk factors for development of DHF. We recommend that in time to come, these factors, with due weight age can form the basis of a clinical scoring system which can be used in admission triage of dengue infected patients.

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