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DENGUE FEVER;
PREDICTORS OF SPONTANEOUS BLEEDING IN DENGUE FEVER

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ABSTRACT… Background: Dengue fever (DF) is a mosquito-transmitted disease caused by the dengue virus, an enveloped, single stranded RNA virus of flaviridae family. DF is widely distributed in many countries of southeast and southern Asia, Central and South America, and the Western Pacific regions. Dengue fever (DF) has emerged as an epidemic in Pakistan for the past few years. **Objectives:** To identify the predictive factors for spontaneous bleeding manifestations in Dengue fever. **Study Design:** Descriptive case series. **Settings:** Pathology department of King Edward Medical University and affiliated hospitals (Mayo Hospital and Lady Aitchison Hospital). **Study Period:** Four months of dengue epidemic July-October 2011. **Material and Methods:** This study included 125 patients with DF. Patients with spontaneous bleeding were identified. Coagulation profile (including platelet count, prothrombin time (PT) and activated partial thromboplastin time (APTT) were recorded in each group (With and without bleeding). **Results:** Spontaneous bleeding during dengue fever occurred in 53(42.4%) patients. The mean coagulation profile in patients of dengue fever with and without spontaneous bleeding was as follows: platelets (91.28±26.64X109/L versus 112.10±17.12 X 109/L, p<0.05), PT (15.72±2.42 versus 14.47±3.70 seconds, P>0.05), and APTT (41.0±24.00 versus 36.65±4.65 seconds), p<0.05). **Conclusions:** Frequency of spontaneous bleeding in DF was high. A raised APTT and lower platelets counts was found in patients of dengue fever with bleeding as compared to non bleeders while no difference in PT levels in both groups.

Key words: Bleeding, Coagulopathy, Dengue Fever, Platelets Count.

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INTRODUCTION

Dengue fever (DF) is a mosquito-transmitted disease caused by the dengue virus, an enveloped, single stranded RNA virus of flaviridae family.[1] DF is widely distributed in many countries of southeast and southern Asia, Central and South America, and the Western Pacific regions. The World Health Organization (WHO) considers DF a major international health threat. The ongoing impact is staggering. It is estimated that there are more than 100 million cases of dengue worldwide every year.[2] It is an infectious tropical disease caused by the dengue virus and is spread by the bite of mosquitoes, most commonly the mosquito Aedes aegypti, which is found in tropic and subtropic regions.[3] Dengue infection is caused by any of 4 different serotypes of the virus (DEN-1, DEN-2, DEN-3, and DEN-4).[4] DF is a severe, flu-like illness that affects infants, young children and adults. Common presentation is high grade fever typically accompanied by any of the following: chills, retro-orbital pain, photophobia, backache, severe muscle ache and joint ache, nausea, vomiting, abdominal pain. Other signs and symtoms include a generalized maculopapular rash, lymph node enlargement, hepatosplenomegaly, petechiae, and other hemorrhagic manifestations, such as epistaxis and gastrointestinal bleeding. Clinical presentation may vary from undifferentiated fever, classic dengue fever (DF), Dengue hemorrhagic fever(DHF) to Dengue shock syndrome(DSS).[5] DHF is a more serious form of DF, characterized by sudden onset of fever as well as bleeding (often severe) from mucosal surfaces (e.g., nasal, gastrointestinal, vaginal, gums), liver enlargement, and in severe cases, circulatory failure. DHF is associated with abnormal blood

clotting, low platelet count (thrombocytopenia), and evidence of plasma leaking through capillaries. Dengue shock syndrome (DSS) includes all of the criteria for DHF described above, as well as life-threatening hypotension (severely reduced blood pressure, shock). DHF generally occurs in people with a history of exposure to multiple dengue virus serotypes, and the partial immune reaction contributes to the severity of the disease.[6] Spontaneous bleeding is an important cause of hospitalization in dengue patients. In the year 2011 Pakistan witnessed an epidemic on a very large scale, although this disease had been occurring in the last couple of years, but this time it was a big outbreak. This study highlights the laboratory predictors of hemorrhage. This can help us to differentiate between the patients that need more aggressive management than patients who can be treated conservatively.

MATERIAL AND METHODS

For this descriptive case series, 125 patients both males and females of all ages diagnosed as Dengue fever (High grade fever and IgM positive by ELISA for Dengue antibodies) were included in study. Patients with chronic liver disease, chronic renal failure, recent trauma, congestive cardiac failure and patients with any acquired or congenital bleeding disorder were excluded from the study. After taking informed consent and ensuring their confidentiality laboratory tests were carried out. For Complete blood count (CBC), blood samples were collected on 3rd day of fever in EDTA vials and were run on sysmex KX-21 to assess platelet count. Peripheral smears were prepared and stained with Giemsa stain to examine platelet count. For Prothrombin Time (PT), blood samples were on 3rd day of fever taken in Na-citrate vial and clotting time were noted after addition of thromboplastin. For Activated partial thrromboplastin time (Aptt) blood samples were performed on 3rd day of fever taken in Na-citrate vial, clotting time were noted after activation of contact factors with alexin.

Patients were followed during hospital stay to record any bleeding episode for determining the frequency of bleeding. Then levels of PT, APTT and platelets count were recorded in each group (With and without bleeding). Data was entered and analyzed on SPSS version 18.Quantitaive variables including platelet count, PT, APTT, day of fever were presented as mean ± S.D. Qualitative variables including gender, spontaneous bleeding (yes/no) were presented in the form of frequencies and percentages.

RESULTS

In the study, the mean age of the patients was 39.62 + 14.36 years [range 10 – 88].There were 85 (68%) male patients and 40 (32%) female patients in the study Figure-1. The female to male ratio was 1:2.1. Bleeding was present among 53 (42.4%) patients and was not present among 72 (57.6%) patients of dengue fever during hospital stay. The mean platelet count in patients with bleeding was 91.28±26.64 X 109/L, while in those without bleeding was 112.10±17.12 X 109/L. This difference was statistically significant i.e. $p<0.05$. The mean PT in patients with bleeding was 15.72±2.42 seconds while in patients without bleeding was 14.47±3.70 second in patients without bleeding. Statistically, this difference was not significant. The mean APTT in patients with bleeding was 41.02+4.00 seconds while in those without bleeding was 36.65+4.65 seconds. Statistically, this difference was significant ($p<0.05$). (Table-I)

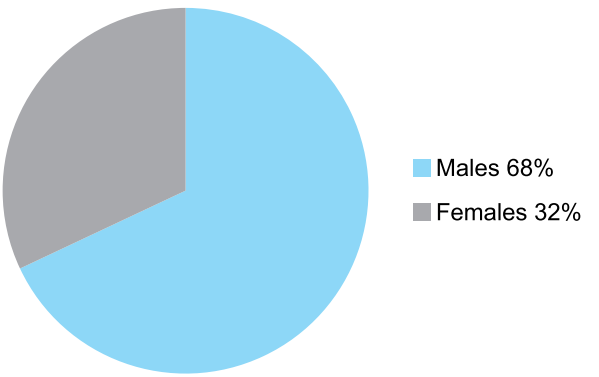

Figure-1. Gender distribution. (n=125)

DISCUSSION

In Pakistan, dengue fever has been recognized as an epidemic since 2011. This study was conducted in patients with dengue fever to determine the frequency of spontaneous bleeding and pattern of coagulation profiles associated with it.

Laboratory Values	Patients Distribution		P-value*
	Patients with Bleeding (n=53)	Patients without Bleeding (n=72)	
	Mean ± SD	Mean ± SD	
Platelets	91.28±26.64	112.10±17.12	0.000**
PT	15.72±2.42	14.47±3.70	0.078***
APTT	41.02±4.00	36.65±4.65	0.000**

Table-I. Comparison of mean laboratory values of Dengue fever patients with and without bleeding (n= 125)
* Student's t-test ** Statistically significant *** Statistically not significant

The coagulation profile has also been studied in past by some other studies. The mean age of the patients in our study was 39.62 + 14.36 years. These results are consistent with the studies conducted by Muniraja PK, et al, and Itha S, et al, of India in which the mean age of the patients was 35±12.8 years and 33 years respectively, and Riaz MM, et al, of Pakistan in which the mean age of the patients was 31±12.9 years. This reflects that usually adult population is effected more with dengue fever which may be due to the fact that adult population has more environmental exposure.[6,8,9]

The majority of the patients in my study were males 68%, while 32% were female. This male predominance is also witnessed by Itha S, et al, (64.4% male versus 35.6% female) and Riaz MM, et al, (60% male versus 40%) female. Muniraja PK, et al, also observed that 60% patients in their study were males. Chowdhary R, etal, observed a higher frequency of male (70%) versus female (30%). These observations show that there is a male dominance over the female among patients with dengue fever. This may be attributed either to the more environmental exposure of males than females or to poor medical facilities for females in our society.[6,8,9,10]

The spontaneous bleeding was observed in 42.4% patients. In study by Riaz MM, et al, the frequency of spontaneous bleeding was 34%. In another study conducted in India, the bleeding manifestations were seen in 50.6% patients. Karoli R, et al also observed hemorrhagic manifestations in 40% patients. Diaz Quijano FA et al, observed that 29.4% patients developed spontaneous bleeding during dengue fever. So, this can be observed that almost one third of the patients with dengue fever develop hemorrhage and this figure may go as high as 50%.[6,7,11] The mean platelets count in patients with bleeding was low i.e. 91.28±26.64 X 109/L as compared to that of patients without bleeding i.e. 112.10±17.12 X 109/L and this difference was statistically significant. Diaz Quijano FA et al also observed a higher mean of platelets count who had no bleeding (146±51 X 109/L vs 190±77.8 X 109/L). In another study by Orsil FA, this was observed that patients with DF and bleedings had lower platelet counts than DF without bleeding (median = 195×109 vs 203×109, P<0.0001).[7,12]

The mean prothrombin time was not significantly different in patients with and without bleeding i.e. (15.72±2.42 seconds in patients with bleeding and 14.47±3.70 second in patients without bleeding. Diaz Quijano FA et al also did not find any difference of mean PT values in patients of dengue fever with and without spontaneous bleeding i.e PT (15.6±0.6 seconds vs 15 ±0.8 seconds).[7] The patients with spontaneous bleeding had higher APTT value i.e. 41.02±4.00 seconds as compared to those without bleeding 36.65±4.65 second. While in study by Diaz Quijano FA et al , mean APTT was a little higher than those without spontaneous bleeding i.e. (34±1.3 seconds vs 32.2±1.4 seconds). In study by Saha AK, et al, APTT was raised in 54.4% bleeders as compared to non-bleeders among dengue fever patients with an odds ratio of 12.8667 at 95% confidence interval, which was very significant.[7,13] So, it was observed that not all the coagulation parameters are deranged in patients with dengue fever; rather the patients with dengue fever without bleeding may have a tendency towards normal coagulation profile. PT was not found to be deranged in both studies i.e. mine and that of Diaz Quijano FA, et al.

CONCLUSION

We concluded that the frequency of spontaneous bleeding is very high among patients with dengue fever. There is significant difference of platelet count and APTT in patients with and without bleeding. So, platelets counts and APTT levels may be helpful in detecting high risk patients for developing bleeding in dengue fever. However, more studies with large sample size are suggested to determine the predictive values of these investigations.

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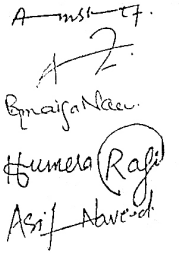
1	Ammarah Sharif	Main Author	
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