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Role of Platelet Indices in Patients with Dengue Infection in Red Sea State, Sudan

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Abstract: ***Dengue is a global endemic and most prevalent human arbovirus disease. Recently, platelet indices have been assessed usefully in the diagnosis conditions with abnormal platelet counts. A case control study was conducted to investigate and assess the role of platelet indices in patients with dengue infection in Red Sea State, Sudan. Platelet counts (PLT), mean platelet volume (MPV), platelet distribution width (PDW) and platelet large cell ratio (P-LCR) were measured. MPV and PLT were significantly lower in cases of dengue (P<0.000). The PDW and P-LCR were significantly high in cases of dengue (P<0.000 and 0.431 respectively). Low PLT, MPV and PDW may be used as probable indicators for dengue in endemic area. MPV <9 fl and PDW >13fl shows considerable sensitivity for dengue fever.***

Keyword: Mean platelet volume, Dengue, thrombocytopenia, Platelet distribution width, Sudan

1. Introduction

Dengue fever (DENV) is the most rapidly spreading mosquito-borne viral disease in the world. An estimated 50 million infections per years occur across approximately 100 countries. Incidence has increased 30-fold with increasing geographic expansion with potential for further spread [1]. The primary dengue vector *Aedes aegypti* mosquito has become widely distributed across tropical and subtropical latitudes. Based on the antigenic difference, DENV can be divided into four different serotypes, DENV 1 – 4 [2]. The resurgence of dengue has been observed in Port Sudan, Red Sea State, Sudan and dengue outbreak have been frequently reported from different part of the state in both urban and rural populations [3, 4]. Severity of the illness is determined by various risk factors such as age, pre-existing illness, infecting serotype, and secondary infection. A second infection with a different serotype leads to more severe form of the disease than the primary infection [5]. One of the most common laboratory findings in dengue is thrombocytopenia [2]. The complex mechanism of thrombocytopenia remains unclear. Possible mechanisms of thrombocytopenia could be, direct bone marrow suppression by the virus; anti-dengue antibody-mediated platelet destruction, peripheral consumption of platelets and isolated viral replication in the platelet. Thrombocytopenia leads to bleeding although the platelet count may not directly correlate with the bleeding manifestation [6]. Recently, novel platelet indices such as MPV, PDW, and P-LCR have been investigated as prospective platelet activation markers [7].Platelet volume, a marker of platelet function and activity is measured as mean platelet volume (MPV) by hematology analyzers. MPV can be used as independent predictors of bleeding. It is surrogate marker of bone marrow activity; a high MPV indicates increased megakaryocyte activity. A low MPV indicates marrow suppression and increased risk of bleeding. Correlation of platelet count and MPV with bleeding and severity of the disease can potentially predict outcome [8] Platelets with increased number and size of pseudopodia differ in size, possibly affecting platelet distribution width (PDW) which increases during platelet activation [7]. P-LCR was significantly decreased in patients with thrombocytosis than in normal while it was increased in thrombocytopenia. P-LCR was inversely related to platelet count and directly related to PDW and MPV [9]. The aim of our study was to investigate the platelet indices in patients compared to the control and to assess the role of it in dengue infection.

2. Material and Method

This study was conducted prospectively for a period from February 2013 to June 2014 during the recent outbreak of dengue in Port Sudan teaching hospital, Red Sea State, Sudan. The platelet parameters were measured by the Sysmex KX-21N (Sysmex Corporation, B 7151, MF 9/2008, Japan) semi automated hematology analyzer on venous samples collected in K_3EDTA from 334 patients as a clinical sample and 101 apparent healthy normal individuals as control sample. The inclusion criteria were all patients with clinical features and serologically positive dengue infection included. The exclusion criteria include patient's serologically negative dengue and if routine laboratory testing suggested a bacterial, parasite or any viral infection other than dengue infection or any other disease. The specimens were analysed within 1 hour from venesection. The parameters analysed included PLT, MPV, PDW and P-LCR. Observations based on the MPV were considered valid only if the specimens were analysed within 1 hour from venesection, to avoid the problems occurring when EDTA collected samples are analysed.

Patients were classified as dengue fever, dengue hemorrhagic fever or dengue shock syndrome according to WHO guidelines and laboratory diagnosis of dengue was established by demonstration of IgM and IgG immune

chromatographic Rapid strip test (BioTracer/BioFocus, REF: 17112, Exp.12/2015, Korea), sensitivity 95.6 and specificity 96.

Statistical analysis

Data were analyzed using a Computer Statistical Package for Social Sciences (SPSS) program version 20 (IBN. Chicago, USA). Measurements of laboratory data platelet parameters of patients with DF, DHF were statistically tested by compare mean and Chi-square test which ever was appropriate. A *P.value* less than 0.05 were considered statistically significant. The sensitivity and specificity of relevant platelet indices parameters as an indicator of dengue infection were also assessed by performing receptor operating curve (ROC) analysis.

Ethical Consideration

Ethical clearance of this study was approved from the regional Ethical Review Committee (ERC). Data regarding the age and sex was recorded in predesigned forms.

3. Result

This is a case control analytical study conducted in Port Sudan teaching hospital, Red Sea State, Sudan. The total number of the confirmed diagnosed dengue patients was 334. The age of the patients in this study was between 3 – 80 years (mean age 30 years). 101 individuals, age and sex matched, were selected as control group. The control individual aged between 6 – 76 years (mean age 22 years). Of the 334 clinical patients, (217) 65% were males and (117) 35% were female. In control group, (64) 63.4% were males and (37) 36.6% were females. Demographics data were obtained from patients with dengue virus infection include residence, tribe, and occupation. The eastern part of the study area (Selalab) represented the highest incidence (27.2%) region affected by dengue virus infection. The student was the most common segment of occupation affected (34.74%), followed by traders (18.73%), and the house wife (18.13%). Table 1 illustrates that the overwhelming majority of dengue virus infection is among the Northern Sudan tribe (43.1%), followed by the Hadandwa tribe (21%), Bani amer tribe (18.3%), western Sudan tribe (14.7%), and the immigrants tribe (3%). All of the Patients 334 presented was analysed for PLT, MPV, PDW, and P-LCR. Median MPV was 10.49 (range 7.0 – 16 fl), median PDW was 15.56 (range 8.1 – 23 fl), median P-LCR was 31.13 (range 8.5 – 49.6%), median PLT was $95x10^9$/l (range $3x10^9$/l – $443x10^9$/l). Low MPV which indicates bone marrow suppression was noted in 16.6% of patients with DF and 22.2% in patients with DHF. A high PDW which indicates as useful marker for platelet activation was seen in 28% of patients with DF and 26.7% in DHF patients. High P-LCR that correlated with thrombocytopenia was observed in 15.6% of patients with DHF and 11% in DF patients (Table 2). The differences between the patient group and the control group in MPV and PLT were found to be significantly lower in the patient group (P< 0.000), while the differences between patient group and control in PDW and P-LCR were found to be significant higher in patient group (P< 0.000, 0.431 respectively) (Table 3). There was significant of MPV with PLT, PDW, and P-LCR (P< 0.002 and 0.000, 0.000 respectively). The relationship of the platelet indices with bleeding and thrombocytopenia are summarized in (Table 4). 279 (83.9%) of the patients had thrombocytopenia. Thrombocytopenia was found more severe with bleeding individuals (P< 0.000). Table 5 shows that platelet count was more sensitive for DF and DHF (100%) but had positive predictive value for DF 84%. In addition, low MPV, high PDW, and high P-LCR are comparatively more sensitive, specific, and positive predictive value for DF than DHF.

Table 1: Frequency of DF/DHF in different (Red Sea State) tribes

Tribe	Number	Frequency %
Western Sudan	49	14.7
Bani Amer	61	18.3
Northern Sudan	144	43.1
Hadandwa	70	21.0
Immigrants	10	3.0
Total	334	100

Table 2: Platelet indices in the case group of the study

Diagnosis	Low MPV	High MPV	Normal MPV	Total
DF	48 (16.6%)	2 (0.7%)	239 (82.7%)	289 (86.5%)
DHF	10 (22.2%)	0	35 (77.8%)	45 (13.5%)
Total	58 (17.4%)	2 (0.6%)	274 (82%)	334 (100%)
	Low PDW	High PDW	Normal PDW	Total
DF	13 (4.5%)	81 (28%)	195 (67.5%)	289 (86.5%)
DHF	2 (4.4%)	12 (26.7%)	31 (68.9%)	45 (13.5%)
Total	15 (4.5%)	93 (27.8%)	226 (67.7%)	334 (100%)
	Low PLCR	High PLCR	Normal PLCR	Total
DF	13 (4.5%)	32 (11.0%)	244 (84.4%)	289 (86.5%)
DHF	2 (4.4%)	7 (15.6%)	36 (80%)	45 (13.5%)
Total	15 (4.5%)	39 (11.7%)	280 (83.8%)	334 (100%)

MPV, mean platelet volume; PDW, platelet distribution width, P-LCR: platelet large cell ratio DF, dengue fever; DHF, dengue haemorrhaic fever

Table 3: The difference of platelet indices between case and control groups in the study

Parameters	Test group (mean)	Control group (mean)	P-value
MPV	7.03	10.56	0.000
PDW	2.2335	2.0693	0.000
P-LCR	2.0719	2.0396	0.431
Platelet count	95691	219099	0.000

Table 4: Relationship between the study parameters

Parameters	Bleeding	Thrombocytopenia
	P value	*P value*
Platelet count	0.000	0.000
MPV	0.165	0.813
PDW	0.269	0.238
P-LCR	0.251	0.386

Table 5: Statistical analysis of Platelet indices for diagnosis of Dengue fever (DF) and Dengue hemorrhagic fever (DHF).

Parameters	*Sensitivity (%)*	*Specificity (%)*	*PPV*	*NPP*	*LR*	*95%CI*
PLT						
DF	100	55	84	100	2.22	1.79-2.76

DHF	100	19	16	100	1.24	1.17-1.31
MPV <9fl						
DF	96	96	83	99	23.9	12.99-43.99
DHF	83	42	17	95	1.44	1.05-2.97
PDW >13fl						
DF	86	94	87	94	14.86	8.53-25.90
DHF	48	71	13	94	1.64	1.05-2.56
P-LCR >43%						
DF	71	97	82	95	25.5	12.0 – 54.18
DHF	86	53	28	95	1.82	1.31 – 2.54

PPV, Positive Predictive Value; NPV, Negative Predictive Value; LR, Likelihood Ratio; CI, Confidence Interval; PLT, Platelet Count; MPV, Mean Platelet Volume; PDW, Platelet Distribution Width

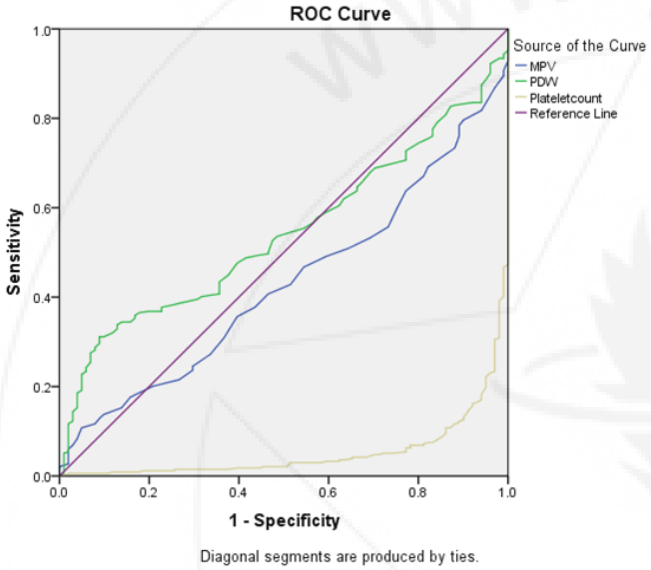

Figure 1: Receptor operating characteristic (ROC) curve of platelet count, MPV, and PDW for dengue infection

4. Discussion

Platelets are involved in hemostasis, tissue repairing, and infection. To our knowledge, there are no studies investigating changes in platelet indices during dengue infection as a useful marker in our region. Among values in platelet indices during dengue infection, we believe that variations in the platelet indices are suitable for evaluation. MPV has been evaluated as a diagnostic tool in different conditions with thrombocytopenia with contradictory results. It has been demonstrated that MPV has sufficient sensitivity and specificity to discriminate aplastic anemia, bone marrow disease, hypoproductive thrombocytopenia, and bone marrow metastasis of solid tumor [8 – 11]. However, it has been reported that although MPV may be used as an initial suggestion of bone marrow disease in thrombocytopenic patient, it has limited sensitivity and specificity [12]. As the platelets are natural sources of growth factors like platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF-1) or transforming growth factor β (TGF-β), they have important role in inflammation, angiogenesis, repair and regeneration of the tissues [13]. The activation of the platelets causes some morphological alterations: the activated platelets seem larger by becoming spherical in shape and forming pseudopodia. As a result, platelets with enhanced number and size of pseudopodia will be different in size leading alterations in PDW [7]. In our study we found that MPV and Platelet count were lower in dengue fever patients when compared to controls. In contrast, PDW levels were higher in dengue fever patients compared to controls. However, the alteration in MPV level in dengue infection was studied before by Wiwanikit V. We noticed that MPV level was significantly lower and PDW level was significantly higher in the dengue fever, which reflect that decreasing MPV and increasing PDW levels may predict dengue fever.

Other researchers such as Niethammer et al have upheld the diagnostic value of platelet histogram maximum rather than MPV to differentiate between idiopathic thrombocytopenic purpura (ITP) and hypoproductive thrombocytopenia [14, 15]. Ntiaos et al have found a combination of MPV and PDW to P-LCR [16]. A different approach was adopted by Kurata et al who assessed reticulated platelet which are newly released from the marrow by using RNA-binding dyes and flow cytometric analysis, these immature platelets were successful as a discriminating guide to determine the etiology of thrombocytopenia [17].

5. Conclusion

In conclusion, significant differences were observed in the MPV, PDW and PLT in patients with dengue infection, low platelet count, MPV, and PDW may be used as probable indicators for dengue in endemic area. Low MPV <9 fl and high PDW >13fl shows considerable sensitivity for dengue fever.

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