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Cytopenia in dengue fever and their associations: A Cohort Study

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A B S T R A C T

Introduction: Dengue fever is endemic in countries like Pakistan and has multiple complications. Leukopenia and thrombocytopenia are common cytopenia that sometimes lead to complex outcomes. So, we considered it essential to find the associations of dengue-related cytopenia and planned this study.

Methodology: An observational, retrospective cohort study was conducted at Shifa International Hospital Islamabad. 125 patients from the inpatient department diagnosed with dengue fever based on clinical presentation and positive dengue non-structural protein 1 (NS1) were enrolled. Their vitamin B12 levels, minimum values of TLC (total leukocyte count), and platelet counts during admission were found in their records. All information was entered and analyzed using the SPSS 23 version. After descriptive statistics, Patients' age, gender, residence, and B12 levels were cross tabulated against the TLC and platelet count values using the chi-square test. The descriptive results were expressed in percentages, while chi-square was described as a $p < 0.05$, considered statistically significant.

Results: 125 patients with dengue fever were included in the study; 73 (58.4%) were male, and 52 (41.6%) were female. The mean age was 42.8, the mean B12 level was 94.3 pmol/L, the mean platelet count was 57,000/ µL, and the mean TLC was 5084.8/ µL. Age, gender, residence, and B12 levels did not affect leukopenia and thrombocytopenia in dengue patients ($p > 0.05$).

Conclusion: Dengue-related cytopenia is not correlated with the differences in age, gender, residence and B12 levels and mandates further research work.

Keywords: *Dengue fever, Cytopenia in dengue, Thrombocytopenia in dengue, Leukopenia in dengue, B12 deficiency in dengue.*

Introduction

Dengue is an acute viral illness caused by the RNA virus of the Flaviviridae and spread by Aedes mosquitoes.[1] It is predominantly distributed in tropical and subtropical regions that are the natural home for its vector. Humans and mosquitoes are the only two known hosts.

Clinical presentation of dengue fever Infection with any of the 4 dengue virus serotypes results in a diverse range of symptoms, from mild undifferentiated fever to life-threatening hemorrhagic fever and shock.[2] Cytopenia, particularly thrombocytopenia, is the well-known presentation of dengue fever. It concerns the severity of severe thrombocytopenia in 11.5% of the cases.[3] Dengue fever is classified, in order of increasing severity, as dengue fever (DF), dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS). More recently, the WHO proposed a revised classification of clinical Infection: dengue, dengue with warning signs, and severe dengue. It is a self-limiting infection but can often progress to a life-

threatening shock syndrome.[4] The detection of NS1 is quite helpful for early detection of dengue fever.[5]

Different studies have described various predisposing factors responsible for dengue-related thrombocytopenia. Castilho BM and colleagues concluded that older age, male gender, and higher MCH are risk factors.[4] Ravichandran S et al. have identified ABO blood groups for dengue-related complications.[6] Take S et al., in their study, concluded that low B12 levels can cause dengue-related severe thrombocytopenia.[7] Since B12 deficiency is quite prevalent in our country and thrombocytopenia and even leukopenia are well-recognized hematological effects of B12 deficiency, it is logical to think about the possible connection between B12 deficiency and dengue-related cytopenia. So, we planned this study to see the effect of age, gender, urban or rural residence (considering nutritional differences among them) and B12 levels on dengue-related cytopenia to find solutions related to anticipating and managing dengue complications.

Methodology

After obtaining due permission and protocol approval from the IRB & Ethics Committee of Shifa International Hospital Islamabad (IRB No.=035-855-2020), all dengue patients meeting inclusion criteria were included those who presented to Shifa Hospital in dengue season 2020 and 2021. Patients with diagnostic discrepancies, known cytopenia, chronic liver disease, chronic kidney disease, on cytotoxic drugs, taking steroids, taking antiplatelet medicines or anti-coagulants, were excluded due to the expected disease-modifying effect. Patients who did not have their B12 levels done were also excluded from the study. The details of patients' demographic features like age, gender, and residence (urban or rural) were noted down. Patients' daily TLC (total leukocyte count) and platelet count values were followed from their records, and minimum values were reported.

B12 levels were also noted down from their record. TLC count<4000/µL was considered low (leukopenia). While platelet count<150000/µL was considered insufficient (thrombocytopenia). B12 levels <25 pmol/L were deemed inadequate. All information was entered, and IBM-SPSS version 23 was used for statistical analysis. The descriptive stats were calculated for both qualitative and quantitative data. For qualitative data like gender and residence, % ages, tables, and figures were presented. Range and means were calculated for quantitative data like age and laboratory values. To see the effect of age, gender, residence and B12 levels on minimum noted TLC and platelet count, a chi-square test was applied and expressed as a $p<0.05$ with a 95% confidence interval considered statistically significant.

Results

The 125 patients with dengue fever were included in the study, of which 73(58.4%) were male and 52(41.6%) were females. The mean age was 42.8 (15 to 84 years), the mean B12 level was 94.3 (12 to 265 pmol/L), the mean platelet count was 57,000 (5000 to 265000/µL) and the mean total leucocyte count was found to be 5084.8 (660 to 17300/ µL). Among the category of severity of dengue fever, 107(85.6%) had dengue fever, 17(13.6%) had dengue hemorrhagic fever, and only one (0.8%) patient presented with dengue shock syndrome. Baseline characteristics of patients (Table 1).

We observed the effect of different variables on the category of cytopenia (monocytopenia or bicytopenia). Demographic features, age, gender, and residence did not affect the type of cytopenia (p-values 0.592, 0.249, and 0.588, respectively). B12 levels also did not affect the development of either monocytopenia or bicytopenia ($p = 0.559$). However, 80% of patients above 70 developed only Monocytopenia (Table 2). We then computed results to see the effect of different variables on values of TLC count (minimum TLC count during admission). The demographic features, age, gender, and residence did not affect the TLC count (p-value 0.368, 0.176, 0.589, respectively). B12 levels also did not affect the value of TLC ($p = 0.632$). However, it was noted that 80% of the patients with ages above 70 years did not develop leukopenia (TLC <4000/µL) (Table 3).

We calculated the effect of variables on the platelet count value (minimum platelet count during admission). The demographic features, age, gender and residence did not affect the platelet count (p-value 0.657, 0.911, 0.525, respectively). B12 levels also did not affect the value of TLC ($p = 0.194$). However, it was noted that 90% of patients with age above 70 years did not develop thrombocytopenia (platelet count < 150,000/ µL) (Table 4).

Table 1: Baseline characteristics of the study population (n = 125)

Baseline characteristics		Frequency	Percentage
Gender	Male	73	58.4
	Female	52	41.6
Age (Years)	15-30	39	31.2
	31-50	42	33.6
	51-70	34	27.2
	>70	10	8.0
Residence	Urban	103	82.4
	Rural	22	17.6
TLC (per µL)	<4000	56	44.8
	>4000	69	55.2
Platelets (per µL)	<150	33	26.4
	>150	92	73.6
Category of Cytopenias	Monocytopenia	69	55.2
	Bicytopenia	52	41.6
	None	4	3.2
B12 levels (pmol/L)	<25	18	14.4
	>25	107	85.6

Table 2: Effect of variables on the category of Cytopenia (n = 125)

Variable		Category of Cytopenia			Total	p value
		Monocytopenia	Bicytopenia	None		
Age category (years)	15-30	20 (51.3%)	18 (46%)	1 (2.7%)	39	0.592
	31-50	20 (47.6%)	20 (47.6%)	2 (4.8%)	42	
	51-70	21 (61.7%)	12 (35.3%)	1 (3%)	34	
	>70	8 (80%)	2 (20%)	0 (0%)	10	
Gender	Male	44 (60.3%)	26 (35.6%)	3 (4.1%)	73	0.249
	Female	25 (48%)	26 (50%)	1 (2%)	52	
Residence	Urban	59 (57.1%)	41 (40%)	3 (2.9%)	103	0.588
	Rural	10 (46%)	11 (50%)	1 (4%)	22	
Category of B12 levels (pmol/L)	<25	8 (44.4%)	9 (50%)	1 (5.6%)	18	0.559
	>25	61 (57%)	43 (40.2%)	3 (2.8%)	107	

Table 3: Effect of variables on TLC count (n = 125)

Variable		TLC count (per µL)		Total	p value
		<4000	>4000		
Age category (years)	15-30	20 (51.3%)	19 (48.7%)	39	0.368
	31-50	19 (59.3%)	13 (40.7%)	32	
	51-70	15 (44.1%)	19 (58.89%)	34	
	>70	2 (20%)	8 (80%)	10	
Gender	Male	29 (39.7%)	44 (60.27%)	73	0.176
	Female	27 (52%)	25 (48%)	52	
Residence	Urban	45 (43.7%)	58 (56.3%)	103	0.589
	Rural	11 (50%)	11 (50%)	22	
Category of B12 levels (pmol/L)	<25	9 (50%)	9 (50%)	18	0.632
	>25	47 (44%)	60 (56%)	107	

Table 4: Effect of variables on platelet count. (n = 125)

Variable		Platelet count (per µL)		Total	P value
		<150,000	>150,000		
Age category (years)	15-30	11 (28.2%)	28 (71.8%)	39	0.657
	31-50	11 (26.2%)	31 (73.8%)	42	
	51-70	10 (29.4%)	24 (70.6%)	34	
	>70	1 (10%)	9 (90%)	10	
Gender	Male	19 (26%)	54 (74%)	73	0.911
	Female	14 (27%)	38 (73%)	52	
Residence	Urban	26 (25.2%)	77 (74.8%)	103	0.525
	Rural	7 (31.8%)	15 (68.2%)	22	
Category of B12 levels (pmol/L)	<25	7 (39%)	11 (61%)	18	0.194
	>25	26 (24.3%)	81 (75.7%)	107	

Discussion

We started this study to find out some factors affecting the total leukocyte count and platelet count in patients with dengue fever to grab those factors in the future while treating dengue fever. Most of our patients belonged to the age group below 50 years, with male predominance. These findings support the published literature, as Khan DM also concluded in their study that dengue is more prevalent in younger age groups.[8] Our study concluded that gender and age do not correlate with dengue-related cytopenia. Though not statistically significant, we observed that the elderly population above

70 years were less likely to develop bicytopenia, leukopenia and thrombocytopenia. This is against the observations that have already been published. Castilho BM and colleagues described male gender and elder age as risk factors for dengue-related thrombocytopenia.[4] There might be racial differences or differences in the general health of the elderly population of these two nations that resulted in this research discrepancy.

We intended to see the effect of residence on the dengue-related cytopenia. The reason was the understanding of nutritional differences, which we generally consider among urban and rural citizens.[9,10] This is based on the concept that the rural population eats a purer and natural diet and is considered healthier than the urban. However, our study results showed no difference in dengue-related cytopenia based on residence. This indicates either this myth is wrong or dengue-related cytopenia is unrelated to diets and nutrition.[11]

We also checked the effect of B12 levels on dengue-related cytopenia. Our study results did not find any connection between the two. Most researchers have connected dengue fever-related thrombocytopenia and bleeding manifestations with vitamin B12 deficiency.[12] Sagar V et al. and Kansara Y K et al. concluded similarly in their study when they found a significant positive correlation between the severity of thrombocytopenia and vitamin B12 deficiency.[14] They also treated patients with vitamin B12 supplementation and found improved hematological and biochemical parameters.[15]

However, our study results remained non-significant in this regard. Though we could not find any study supporting our impact, we could find some research on micronutrients in dengue fever. A survey of micronutrients from the perspective of B12 concluded that dengue and non-dengue were not different according to B12 levels.[16] Ahmad S and colleagues found out in their review article that the role of micronutrients in dengue is inadequately studied and needs further work to make clear recommendations. In a recent review article,[17] Langerman SD and colleagues have concluded the same way.[18] So, the role of micronutrients in developing dengue and its related complications still needs to be explored in randomized controlled trials.

This is a small sample study, which limited its impacts. However, our results are collected honestly and accurately. We suggest and aim to do more extensive studies to observe the effects of multiple nutritional and non-nutritional factors to determine the fundamental elements affecting dengue-related cytopenia to make guidelines for effective management.

Conclusion

Dengue cytopenia is not correlated with differences in age, gender, residence and B12 levels. Confirmation of these findings and the search for other correlations between dengue and related complications demand further research work.

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