

DENGUE WITH WARNING SIGNS: HEMATOLOGICAL AND BIOCHEMICAL PROFILE ASSOCIATED WITH AGE AND SEX

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Dengue attacks people in all ages but elderly patients are associated with greater severity and poor outcome. Additionally, males account for a major proportion of dengue patients in the Western Pacific Region. Therefore, we conducted this research to investigate if there is any difference in laboratory alterations by age and sex in dengue patients. A cross – sectional research was conducted in 2017 dengue outbreak in the largest city in northern Vietnam. Patients who were diagnosed with dengue with warning signs and admitted to the hospital were recruited and daily blood count were tested from admission until hospital discharge. Hematological and biochemical results were documented and analyzed by age groups and sex. 109 dengue patients were included. Severe thrombocytopenia was more likely to happen in male elderly patients with normal leukocyte counts obtained during the disease course (OR = 1.095; CI 95% 1.-45 – 1.147; p < 0.001 for age; OR = 4.363; CI 95% 1.582 – 12.034; p = 0.004 for males and OR = 4.147; CI95% 1.009 – 17.044; p = 0.049 for nadir leukocyte level ≥ 4 G/L). Elderly patients had lower platelet levels and higher leukocyte counts than young patients. Thrombocytopenia was more severe in males than females. In critical phase, males had higher levels of liver enzymes than females. Male elderly patients seemed to be related to more severe thrombocytopenia. Liver enzymes levels in critical phase tended to be higher in males.

Key words: dengue, elderly patients, sex, severe thrombocytopenia, elevated transaminase levels

I. INTRODUCTION

Dengue infection is one of the most important mosquito-borne disease with a worldwide distribution [1]. Tropical countries including Vietnam are in endemic areas where dengue infection occurs annually. Its clinical and laboratory manifestations vary depending on phases of illness and its outcome is poor in severe cases without immediate and appropriate treatment [2]. According to WHO Dengue guideline in 2009, dengue is classified into three clinical levels, in which dengue patients with warning signs should be

hospitalized and closely monitored due to their high risk of severe progression. Hematological and biochemical parameters are crucial for prognosis in these cases [2]. While dengue could be transmitted to people living in the endemic regions in a wide range of age, there has been raising concern in elderly patients with dengue in recent researches as they were associated with greater severity, worse outcome and increased risk of mortality [3–7]. Underlying reasons for those associations have not been understood clearly. Moreover, males were reported to be predominant in Western Pacific countries consistently over time [8]. Those findings raised a question if there is any difference by age and gender in laboratory abnormal results among dengue patients.

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Received: 02/04/2019

Accepted: 03/06/2019

With the purpose to explore that question, we conducted a research on dengue patients with warning signs in the 2017 dengue outbreak in Hanoi, Vietnam.

II. METHODS

1. Methods

The cross-sectional study was conducted at National Hospital of Tropical Diseases, in northern Vietnam during the 2017 dengue outbreak. Diagnosis of dengue infection was made by clinical symptoms along with alterations in hematological test and confirmed by either positive NS1 antigen or positive dengue IgM antibody. Dengue patients aged > 16 years old who were admitted during August 2017 due to presence of warning signs- defined by WHO criteria 2009 [2]- were recruited. Exclusion criteria included history of cirrhosis and pre-existing hematologic diseases such as thrombocytopenia or coagulation disorders.

2. Data collection

Dengue inpatients had full blood count at least once a day from admission until discharge. Those daily hematological results, coagulation test, together with biochemical parameters (serum transaminase, urea and creatinine) and daily symptoms (fever, bleeding, vomiting...) were documented for research. Additionally, available blood count results before admission was also collected from medical records and clinical examination.

3. Data Analysis

Data of clinical manifestations and laboratory findings were documented and compared

between age groups as well as between male and female groups. Clinical course of illness were divided into 3 phases, including febrile phase (days 1 – 3), critical phase (days 4 – 6) and convalescent phase (days 7 – 10) for comparison. Comparison between categorical variables were tested by Chi – square test while Mann – Whitney test was used for comparing continuous variables. Logistic regression model was used to test for association between independent factors and risk of severe thrombocytopenia, defined as nadir of platelet counts < 20 G/L. Differences were considered as statistical significance when p value < 0.05. Statistical analyses were performed with SPSS 23 software.

4. Research Ethics

This study was an observational study without any intervention. Patients volunteered to join the study and their information was kept confidential.

III. RESULTS

A total of 109 eligible dengue patients was included. Among them, males were predominant with 58.7%. Median age was 31 years. Patients aged > 50 years accounted for only 11.9% of the study population. In general, the average duration of fever was 5.39 ± 1.49 days. Most patients recovered after 8 - 9 days of illness.

While leukocytes bottomed out on day 5, with a median leukocyte count of 2.47 (IQR: 25 – 41.5) G/L, platelets decreased to the lowest point on days 6 – 7 in 69.8% of patients. There were 16/109 (14.7%) patients whose lowest platelet counts were seen after day 7.

Table 1. Platelet counts on days 5 – 7 of illness compared between age groups

Age groups (years)		17 - 30	31 - 50	> 50	p
Platelet count (G/L) (Median_IQR)	Day 5	66.5 (37.75 – 100.25)	50 (22.75 – 84.75)	15 (12.15 – 39.5)	0.036
	Day 6	48 (31 – 79)	27 (16.5 – 47)	11.45 (7.5 – 32.75)	< 0.001
	Day 7	39 (25 – 63)	27 (18 – 37)	18 (13 – 75)	0.021
Leukocyte count (G/L) (Median_IQR)	Day 5	2.16 (1.64 – 2.7)	2.62 (1.93 – 3.72)	4.3 (2.43 – 6.02)	0.004
	Day 6	2.6 (2.1 – 3.9)	3.5 (2.45 – 4.75)	4.2 (3.54 – 6.03)	0.005
	Day 7	3.8 (2.9 – 5.2)	5.3 (3.3 – 7.9)	6.1 (4.95 – 8.65)	0.002

Differences in platelet count and leukocyte count between age groups through days 5 – 7 of disease were shown in table 1. Patients in older groups had lower platelet levels compared to those in younger groups, whereas leukocyte levels were higher in older groups than younger groups. Those differences were statistically significant with p – values < 0.05.

Table 2. Platelet counts during illness course in males and females

	Platelet count (Median_IQR) (G/L)							
	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
Male	143 (126.75 – 158.25)	99.5 (58.25 – 119.25)	76.5 (27.15 – 114.75)	48.5 (19.75 – 79)	28 (13 – 51.75)	27 (18 – 46)	35 (28 – 44)	62 (29.5 – 102)
	Female	170 (149.25 – 212.75)	139 (79.5 – 186)	105 (69.5 – 129)	67 (27 – 99)	42.5 (23.7 – 70.5)	36.5 (22.5 – 62.5)	42 (27.5 – 67.75)
p		0.101	0.048	0.067	0.087	0.016	0.044	0.272

Table 2 shows a course of platelet level compared between males and females. In general, females had higher platelet levels than males through all course of disease. However, differences were only significant on days 3, 6 and 7 of illness.

Severe thrombocytopenia occurred in 48 out of 109 patients (44%). Patients with leukopenia were less likely to have severe thrombocytopenia when compared with those who had normal leukocyte count (36.8% vs 75%, respectively; p = 0.05). Logistic regression model indicated that age, male gender and absence of leukopenia were factors associated with increased risk of severe thrombocytopenia. Older patients were more likely to have severe thrombocytopenia than younger patients (OR = 1.095; CI 95% 1.045 – 1.147). The probability of having severe thrombocytopenia in males was 4.363 times higher than in females. Severe thrombocytopenia was more likely to be seen in patients without leukopenia (OR = 4.147; CI 95% 1.009 – 17.044; p = 0.049).

Table 3. Logistic regression model of factors associated with severe thrombocytopenia

	OR	CI 95%	p
Age	1.095	1.045 – 1.147	< 0.001
Male	4.363	1.582 – 12.034	0.004
Nadir of leukocyte count \geq 4 G/L	4.147	1.009 – 17.044	0.049

Table 4. Alterations in transaminases level during illness course

	Day 1 - 3	Day 4 - 6	Day 7 – 10
AST (IU/L) Median_IQR	41 (21 – 59)	94 (58 – 200)	183 (82 – 327)
ALT (IU/L) Median_IQR	35 (13.75 – 53.5)	54 (31.5 – 113.75)	121 (49 – 318)
Elevated AST_N (%)	20/37 (54.1%)	73/80 (91.3%)	20/21 (95.2%)
Elevated ALT_N (%)	16/37 (43.2%)	51/79 (64.6%)	17/22 (77.3%)

Both AST and ALT raised slightly from the early stage then elevated moderately in the critical phase and increased remarkably in the convalescent period (Table 4). The percentages of elevated transaminase levels also increased by the course of the disease. On the first 3 days, elevation in AST levels and ALT levels was seen in 54.1% and 43.2% of patients, respectively. Those rates raised to 95.2% for AST levels and 77.3% for ALT levels in the convalescent period. In general, AST had higher rate as well as higher degree in elevated levels when compared with ALT.

In terms of differences in transaminase levels between males and females, table 5 shows higher levels in males than in females. Significant differences were seen on days 1 – 3 as well as days 4 – 6 of illness for AST levels and days 4 – 6 for ALT levels with p – values were 0.025, 0.047 and 0.016, respectively.

Table 5. Transaminase levels in male and female patients during illness course

	Day of illness	Males	Females	p
AST (U/L) Median_IQR	1 – 3	52 (34 – 60)	24 (20 – 45)	0.025
	4 – 6	112.5 (66 – 243)	86.5 (46 – 137)	0.047
	7 – 10	203 (108 – 273)	75 (42 – 353)	0.669
ALT (U/L) Median_IQR	1 – 3	40 (25 – 53)	14.5 (11 – 53)	0.147
	4 – 6	78 (38 – 164)	46 (23 – 83)	0.016
	7 – 10	135 (61 – 310)	43.5 (32 – 627.5)	0.386

Table 6 only shows differences in transaminase levels between age groups on the first 3 days of illness. On those days, transaminase levels were higher in older groups than younger groups. We did not find any differences in rates of elevated transaminase levels either between males and females or between age groups.

IV. DISCUSSION

In the setting of the 2017 dengue outbreak in Hanoi, we conducted this study and focused on differences in laboratory manifestations by age and sex. Demographic features of patients in this research were similar to those in researches conducted in other Asian countries [8, 9], with predominance of males in study population and 31 (25 – 41.5) years in median age. Patients aged > 50 years comprised of 11.9% of adult patients. Dengue incidence in elderly patients has been reported to be low and ranged from 2% - 7%, depending on researches [10–12]. The proportion of elderly patients in our study was relatively higher than that in previous researches which might be due to the exclusion criteria of our study. We did not include children in our study. Duration of fever and patterns of leukocyte counts during the illness course were similar to classic features in dengue [2]. However, besides of 69.8% of patients whose nadir of platelet level was typical on days 6 or 7 of illness, 14.7% of patients had platelet levels declined to the lowest points after the 7th day of disease, which suggests that the critical phase could occur after the 7th day in a small proportion of dengue patients.

Our study found that older patients had a higher leukocyte level and a lower platelet level when compared with younger patients. These differences were significant at p – values < 0.05 on days 5 – 7 of illness. A study done by Kuo et al, showed similar finding in the febrile phase instead of the critical phase [13]. Those findings are partially supported by a study in Singapore which found that patients aged ≥ 60 years were

less likely to have leukopenia than younger patients [10].

According to our research, platelet levels were more likely to be lower in males than females. That led us to a logistic regression in which male gender was one of the factors associated to severe thrombocytopenia, besides age and absence of leukopenia. We found that older patients as well as males were more likely to have severe thrombocytopenia (OR = 1.095; CI 95% 1.45 – 1.147; $p < 0.001$ and OR = 4.363; CI 95% 1.582 – 12.034; $p = 0.004$, respectively) and patients without leukopenia had more probability to manifest severe thrombocytopenia when compared with those with presented leukopenia (OR = 4.147; CI95% 1.009 – 17.044; $p = 0.049$). Meanwhile, there is limited data on the differences between males and females; a rare study in this field which showed a lower rate of platelet count > 40 G/L in males [14] has partially supported our findings. Although our research findings need more supportive evidence, they are helpful to explain and to support current available findings from other researches. Many studies have showed a correlation between older age and greater severity with worse outcome [3 – 5]. Therefore, the correlation between age and severe thrombocytopenia in our research would clarify those previous results. In terms of association between leukopenia and severe thrombocytopenia, it could also support results from a study in Thailand, which showed a higher leukocyte count and fewer leukopenia on admission in patients with severe dengue

infection (dengue hemorrhagic fever grade II or worse) when compared with those who had mild dengue infection [15].

With regard to biochemical manifestations in dengue infection, elevated transaminase levels are common [16]. In our research, the rates and degrees of elevated transaminase levels increased by the course of disease with the highest rates and the highest levels were seen in convalescent period. AST levels were observed to be higher than ALT levels and elevation rates were also higher in AST levels than ALT levels. These findings were similar to findings in previous researches [13, 17, 18]. We found a significant higher in transaminase levels in older groups than younger groups on the first 3 days which were similar to findings in a study of Kuo, et al [13]. Our research also found higher AST and ALT levels in males than females but significant differences were only seen in days 4 – 6 for both enzymes. In contrast to our results, Souza, et al showed no difference in transaminase values between males and females but females did show a higher rates in elevated transaminase levels than males. However, Souza research study included fewer males than females and there was only recorded transaminase levels on admission. There was no analysis of transaminase levels during the course of disease.

There are several limitations in our study. Although this research was about hematological manifestations in dengue patients with warning signs, we excluded hematocrit levels because of the variation of this parameter with age and sex. Moreover, we did not include children, therefore the differences between age groups were only limited in adults. These limitations need further investigations.

V. CONCLUSION

Our research revealed correlations between

laboratory manifestations and differences in age and sex of dengue patients. Age, male gender and absence of leukopenia during the illness course were associated with severe thrombocytopenia. Older patients had lower platelet levels but higher leukocyte levels and transaminase levels when compared with younger patients. Similarly, males had higher AST and ALT levels in critical phase but lower platelet values when compared with females.

Acknowledgements

We gratefully acknowledge the Board of directors of National Hospital of Tropical Diseases and all the staff of the Department for Viral and Parasitic Diseases for their supports. We specially thank Ha Duc Nguyen for his assistance in data collecting.

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