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Coronavirus Pandemic

Dengue virus serotypes and related factors in children with dengue hemorrhagic fever in Southern Vietnam

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Abstract

Introduction: After the Coronavirus Disease 2019 pandemic, a high number of cases and severe dengue in children were reported in some provinces in the south of Vietnam. This study aimed to determine the distribution of dengue virus serotypes and their correlation with demographic factors, disease severity, clinical manifestations, and laboratory findings.

Methodology: This study employed a cross-sectional design. Ninety-six dengue-infected children admitted to Can Tho Children's Hospital between October 2022 and March 2023 were included. Confirmation of dengue infection was achieved through the real-time polymerase chain reaction (RT-PCR).

Results: Among the identified serotypes, DENV-2 accounted for the highest proportion (71.87%), followed by DENV-1 (23.96%), and DENV-4 (4.17%). DENV-3 was not detected. No significant demographic, disease severity, or laboratory differences were observed among the identified dengue serotypes. However, DENV-2 was associated with a higher occurrence of mucous membrane hemorrhages and gastrointestinal bleeding compared to other serotypes.

Conclusions: Although DENV-2 was the most prevalent serotype responsible for dengue in children in southern Vietnam, it did not lead to more severe cases compared to other serotypes. This finding is crucial for evaluating the illness's prognosis.

Key words: Dengue hemorrhagic fever; dengue virus serotypes; dengue.

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Introduction

Dengue hemorrhagic fever (DHF) is a viral infection caused by the dengue virus (DENV) and is transmitted to humans through the bites of infected Aedes mosquitoes, primarily *Aedes aegypti* [1]. Dengue poses a significant health, economic, and social burden in tropical and subtropical countries, particularly in Southeast Asian countries such as Vietnam. According to the World Health Organization (WHO), there are 390 million dengue virus infections each year, with 96 million cases exhibiting clinical manifestations, and 3.9 billion people are at risk of dengue virus infection [2]. Infection with DENV can be asymptomatic or result in life-threatening conditions such as dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS). There are four serotypes of the dengue virus: DENV-1, DENV-2, DENV-3, and DENV-4. All four serotypes can influence clinical manifestations, laboratory results, and the severity of DHF [3].

The Coronavirus Disease 2019 (COVID-19) pandemic and its consequences have been extensively studied [4,5]. Following the pandemic, there has been a significant increase in the number of dengue cases and their severity, particularly among children, in many provinces in Southeast Asia, including Vietnam [6]. The reason behind this outbreak remains unknown. Debate surrounds whether infection with different serotypes contributes to the severity of the illness. Therefore, we conducted this study to determine the prevalence of each dengue virus serotype and its

correlation with demographic factors, disease severity, clinical manifestations, and laboratory findings in dengue-infected children from Vietnam. We hope that these findings will assist clinicians in the diagnosis, treatment, and prognosis of DHF.

Methodology

Subjects

All children who were diagnosed with DHF and admitted to the Department of Dengue hemorrhagic fever at Can Tho Children's Hospital, the largest pediatric hospital in the Mekong Delta, southern Vietnam, from October 2022 to March 2023 were enrolled in the study.

Inclusion criteria

1. Children from 2 months to 16 years old were diagnosed with DHF according to World Health Organization (WHO) standards 2009 [1]: Patients who were living in or traveling to dengue endemic areas with sudden onset of high fever for 2–7 days and met two of the following criteria:
   i. Nausea, vomiting
   ii. Skin congestion, rash
   iii. Muscular pain, joint pain, and orbital pain
   iv. Positive tourniquet test, cutaneous petechiae/purpura
   v. Hematocrit normal or increased
   vi. The white blood cell (WBC) count is normal or decreased.
   vii. Platelets are normal or decreased.
2. Patients had been hospitalized within 5 days of fever onset.
3. Children whose families approved of joining the study group.

Exclusion criteria

Patients who had been diagnosed with one of the following diseases: hepatic failure, heart failure, renal failure, nephrotic syndrome, or congenital heart disease before DHF this time.

Ethics

This study was approved by the Institutional Review Board Committee for Ethics Committee in Biomedical Research of Can Tho University of Medicine and Pharmacy, Can Tho City, Vietnam (No. 23.107.HV/PCT-HĐĐĐ).

Study design

All children who met the sampling criteria were included in the study. For each sample, the demographic data such as age, and gender, along with the clinical symptoms were recorded, and some tests such as platelet count, and hematocrit (Hct) using SIEMENS ADVIA® 2120i hematology analyzer (Siemens Healthineers, Erlangen, Germany); serum Aspartate Transaminase (AST), Alanine Transaminase (ALT) and albumin levels using AU480 biochemical analyzer (Beckman Coulter, Brea, California (CA), USA, were performed.

At the same time, 3 mL of blood samples were collected using EDTA-containing tubes and sent to Vietnam Research and Development Institute of Clinical Microbiology, Laboratory of Nam Khoa Biotek Company, Ho Chi Minh City, Vietnam, a laboratory that meets ISO 9001:2015, 13485:2017 and WHO-GMP (TRS 908, ANNEX 4) standards, for performing Real-time polymerase chain reaction (RT-PCR) to identify DENV serotypes.

The Real-time PCR process is summarized as follows [7]: Firstly, the blood samples were homogenized by taking 3 mL of the specimen and dissolving it in 10 mL of water containing 50 mg of NALC (N-Acetyl L-Cysteine). Then, the blood samples were immediately centrifuged at the highest speed for 15 minutes and then removed the residue (about 300 µL) to extract the DNA. Nucleic acid extraction was performed using a ZiXpress-32® machine (Zinexts Life Science Corp, Taiwan), using ^{NK}DNARNAprep-MAGBEAD extraction kits manufactured by Nam Khoa company, which was validated by comparison with the BOOM method extraction. Extracted fluid was added into the CFX96 Touch^{TM} system (Bio-Rad Laboratories, USA), using specific primer pairs and specific TaqMan probes to detect four DENV serotypes by Real-time PCR.

Evaluating the results based on the cycle threshold (Ct) value. Ct < 30 is called positive.

Statistical analyses

Statistical analysis was performed with SPSS statistical software for Windows, version 18.0. Data were presented as frequencies or percentages for qualitative variables; mean (or median) and standard deviation (SD) were used for presenting quantitative variables. Comparing the difference between the two ratios based on the Chi-squared/Fisher exact test. Comparing the difference between the two mean values based on the T-test. The multiple-group mean was compared using the ANOVA test (for the normal distribution) and the Kruskal-Wallis test (for the non-normal distribution). The results were considered statistically significant when a p value of less than 5% ($p < 0.05$).

Table 1. Virological and demographic data in patients who tested positive for DENV by Real-time PCR (n = 96).

	DENV-1, n (%)	DENV-2, n (%)	DENV-4, n (%)	Total, n (%)	p_1	p_2
Age (years)						
1-5	3 (3.13)	5 (5.21)	0 (0)	8 (8.34)		
6-10	8 (8.33)	21 (21.87)	1 (1.04)	30 (31.24)	0.587	0.809
> 10	12 (12.5)	43 (44.79)	3 (3.13)	58 (60.42)		
Total, n (%)	23 (23.96)	69 (71.87)	4 (4.17)	96 (100)		
Gender						
Male	8 (8.33)	41 (42.71)	3 (3.13)	52 (54.17)		
Female	15 (15.63)	28 (29.16)	1 (1.04)	44 (45.83)	0.04	0.536
Total (%)	23 (23.96)	69 (71.87)	4 (4.17)	96 (100)		

DENV: Dengue virus; p_1, p_2 were p values when comparing the demographic between DENV-2 and DENV-1, and between DENV-2 and DENV-4, respectively.

Results

Distribution of dengue serotypes among dengue patients

Between October 2022 and March 2023, a total of 327 samples were included in the study. Among these samples, 96 (29.4%) were identified as infected with DENV, with the following breakdown: DENV-1 (23.96%), DENV-2 (71.87%), and DENV-4 (4.17%). No cases of DENV-3 infection were detected (Table 1).

Correlation of dengue virus serotypes with clinical and subclinical manifestations

DHF was most prevalent in children over 10 years old (60.42%), followed by children aged 6-10 years (31.24%), and less common in children aged 1-5 years (8.34%). Among the cases, 54.165% were male, resulting in a male-to-female ratio of 1.18:1 (Table 1).

Table 2 presents the clinical manifestations and disease severity associated with different DENV serotypes in children diagnosed with DHF. The clinical manifestations observed for all three DENV serotypes included cutaneous petechiae (66.7%), nausea and vomiting (46.9%), and muscle and joint pain (34.4%), with no statistically significant differences observed ($p > 0.05$). Mucosal bleeding (18.7%) and gastrointestinal bleeding (2.08%) were fewer common symptoms, but variations were observed among the DENV serotypes. Out of the 96 children positive for DENV, 60.4% had no symptoms of shock, while 39.6% were diagnosed with dengue shock syndrome (DSS). Among the 38 children with DSS, 28 cases were attributed to DENV-2 (73.7%), 8 cases to DENV-1 (21.1%), and 2 cases to DENV-4 (5.2%). When comparing the potential for DSS, the clinical presentations of DSS in DENV-1, DENV-2, and DENV-4 were 34.8%, 40.6%, and 50%, respectively. However, these differences were not statistically significant. The occurrence of DSS was the highest on days 4-5 of illness (36.84% and 34.21%, respectively), followed by day 6 (21.05%). Early DSS cases were rare, with 2 cases occurring on day 3 (5.26%) and 1 case on day 7 (2.63%).

Regarding hematological and biochemical parameters, the highest mean Hct value was observed in DENV-2 patients, while the lowest was found in DENV-1 patients. DENV-4-infected patients exhibited the most significant reduction in serum albumin levels compared to DENV-1 and DENV-2 patients. The median platelet count was lowest in DENV-4 patients and highest in DENV-1 patients. Additionally, median AST and ALT levels were highest in DENV-4 patients

Table 2. Correlation of serotypes with clinical manifestation and disease severity (n = 96).

	DENV-1, n (%)	DENV-2, n (%)	DENV-4, n (%)	Total, n (%)	p_1	p_2
Clinical manifestations						
Petechiae	18 (18.8)	43 (44.8)	3 (3.1)	64 (66.7)	0.161	0.61
Mucosal bleeding	2 (2.1)	13 (13.5)	3 (3.1)	18 (18.7)	0.254	0.008
Gastrointestinal bleeding	0 (0)	1 (1.04)	1 (1.04)	2 (2.08)	0.562	0.005
Nausea/vomiting	13 (13.5)	30 (31.3)	2 (2.1)	45 (46.9)	0.278	0.798
Muscle/joint pain	9 (9.4)	21 (21.9)	3 (3.1)	33 (34.4)	0.441	0.065
Disease severity*						
DHF	15 (15.6)	41 (42.7)	2 (2.1)	58 (60.4)	0.622	0.71
DSS	8 (8.3)	28 (29.2)	2 (2.1)	38 (39.6)		
DSS day*						
Mean ± SD	5.13 ± 1.246	4.64 ± 0.826	5.5 ± 0.707	4.79 ± 0.935		
3rd day	1 (2.63)	1 (2.63)	0 (0)	5.26		
4th day	1 (2.63)	13 (34.21)	0 (0)	36.84	0.204	0.165
5th day	3 (7.89)	9 (23.68)	1 (2.63)	34.21		
6th day	2 (5.26)	5 (13.16)	1 (2.63)	21.05		
7th day	1 (2.63)	0 (0)	0 (0)	2.63		

DHF: Dengue hemorrhagic fever; DSS: Dengue shock syndrome; DENV: Dengue virus; *n = 38, because data were only collected on children with DSS; p_1, p_2 were p values when comparing the clinical manifestation and disease severity between DENV-2 and DENV-1, and between DENV-2 and DENV-4, respectively.

compared to DENV-1 and DENV-2 patients. However, no statistically significant differences were observed in hematological and biochemical parameters within the serotype groups ($p > 0.05$, Table 3).

Discussion

All 327 blood samples from patients with DHF were included in the analysis. The Real-time PCR positive rate was 29.4% (96 out of 327 samples). This result is lower than the study conducted by Phadungsombat *et al.,* who reported a rate of 66.2% during the 2019-2020 epidemic in Hanoi and nearby cities in Northern Vietnam [8]. Kumaria's research also reported a similar rate of 80 out of 320 patients (25%) [9]. This is because Phadungsombat *et al.* collected samples from patients aged 18 years or older with suspected dengue infection and fever (within 5 days of the study); however, acid ribonucleic (RNA) extraction and dengue serotyping were conducted for all positive non-structural 1 (NS1) antigen samples. Both this study and the study by Kumaria included patients with suspected clinical and hematological signs, which may explain the slightly lower rates. During our study period, three DENV serotypes (DENV-1, DENV-2, and DENV-4) were present in Vietnam, with DENV-2 being the predominant serotype and DENV-3 absent. A study by Ngwe Tun *et al.* investigating the circulation of DENV serotypes in children with DHF during the 2017 dengue outbreak in Southern Vietnam reported the most dominant serotype was DENV-1 (52.6%), followed by DENV-4 (23.6%), DENV-2 (4.8%), and DENV-3 (1.3%) [10]. During an outbreak in 2018 in Quang Nam Province, located in the central region of Vietnam approximately 1,000 km from our research site, Phan et al. found the distribution of DENV serotypes to be as follows: 12.82% DENV-1, 17.95% DENV-2, 0.37% DENV-3, 68.5% DENV-4, and 0.37% co-infection with DENV-2 and DENV-4 [11]. In 2014, a study in urban areas of Indonesia reported the presence of all four DENV serotypes, with DENV-2 being the predominant serotype, followed by DENV-1, and DENV-3 being the least common [12]. These findings highlight the regional and temporal variations in the presence of different serotypes during outbreaks.

Regarding the age distribution of DHF cases, our study found that DHF was most common in children over 10 years old (60.42%), followed by children aged 6-10 years (31.24%), and less common in children aged 1-5 years (8.34%). This finding is consistent with the study conducted in Malaysia by Ng *et al.*, which suggested that the odds of being seropositive generally increase with age, with higher rates observed in children aged 5-9 years and 10-19 years [13]. In a study conducted in Bangkok, Thailand, Fried *et al.* reported that the mean age of children diagnosed with DHF was 8.7 ± 3.1 years, and the risk of DHF tends to decline with increasing age in children below 5.4 years but increases with age after 5.4 years [14]. A database of clinically diagnosed and laboratory-confirmed dengue fever cases in southern Vietnam from 2000 to 2015 noted, that the average age of dengue cases with hemorrhage increased from 12.2 ± 8.8 years old (compared to the previous year) to 16.8 ± 13.3 years old from 2000 to 2015. This observation was explained because the longer a person resides in a dengue-endemic area, the higher the risk of dengue infection [15]. Additionally, a higher proportion of male patients were diagnosed with DHF (54.2%), resulting in a male-to-female ratio of 1.18:1. This finding is consistent with the study by Anders *et al.* in Ho Chi Minh City, Vietnam, approximately 170km from our study site, where girls were underrepresented among dengue patients of all severities but experienced higher mortality than boys [16]. Phan QD *et al.* also reported a higher proportion of boys in their study of 74 pediatric patients, with boys accounting for 59.46% [11]. However, a definitive link between specific serotypes and demographic factors has not been established yet.

Different DENV serotypes have been observed to have varying propensities to cause severe forms of the disease. However, there is no clear consensus on the correlation between infecting serotypes and clinical severity. Our study found that mucosal and gastrointestinal bleeding were more common in DENV-

Table 3. Correlation of serotypes with subclinical manifestation (n = 96).

	DENV-1	DENV-2	DENV-4	p_1	p_1
Mean ± Standard Deviation					
Hct (%)	43.0 ± 6.64	44.9 ± 4.77	44.7 ± 3.40	0.142	0.928
*Albumin (g/L)	26.6 ± 4.9	25.6 ± 8.9	19.8 ± 4.7	0.764	0.379
Median (Interquartile Range)					
WBC ($\times 10^3/mm^3$)	67 (11-198)	59 (7-212)	46 (12-98)	0.54	0.474
**AST (U/L)	144.9 (38-940)	151.5 (47.1-2094.4)	3596.8 (100.6-7093)	0.728	0.445
**ALT (U/L)	49.2 (18-387)	65.4 (10.3-500)	1079.35 (38.7-2120)	0.952	0.52

Hct: Hematocrit DENV: Dengue virus; *n = 36, because data were only collected on children with DSS, 2 children were not tested on the level of serum albumin; **n = 42, because liver aminotransferase level tests were designated by the doctor depending on the progress of the disease; p_1, p_2 were p values when comparing the subclinical manifestation between DENV-2 and DENV-1, and between DENV-2 and DENV-4, respectively.

2 infections. In a study conducted in Malaysia, Suppiah *et al.* reported that patients infected with DENV-2 showed significant warning signs and developed severe dengue, with vomiting, epigastric pain, plasma leakage, and shock commonly observed in these patients [17]. Vaughn *et al.,* who undertook a study in Thailand, reached a similar conclusion in their study, where patients with DENV-2 infections had a higher potential for DHF and worse outcomes compared to those infected with other serotypes [18]. However, our study did not find a significant association between disease severity and specific DENV serotypes. This finding is important in assessing the prognosis of the disease, highlighting the need to monitor all DHF cases regardless of the infecting DENV serotypes.

Regarding hematological and biochemical parameters, our study did not find significant differences within the serotype groups. We observed that the mean Hct was higher in DENV-2 infections compared to DENV-1 and DENV-4 infections, although the difference was not statistically significant. A 5-year retrospective study by Kalajanrooj *et al.* conducted at Bangkok Children's Hospital (1995-1999) also reported the highest mean hematocrit in DENV-2 infections and the lowest in DENV-3 infections [19]. Additionally, DENV-4 infections were more associated with liver injury, as indicated by higher AST and ALT levels compared to DENV-1 infections. These findings align with the study by Kalayanarooj *et al.* [19].

Conclusions

Although DENV-2 was the most predominant serotype causing dengue in children in Southern Vietnam, there were no differences observed in disease severity or values of hematological (Hct, platelet count) and biochemical (AST, ALT, serum albumin) parameters compared to other serotypes. This finding is important to assess the prognosis of the illness.

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