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Research Report

THE CHANGING CLINICAL PERFORMANCE OF DENGUE VIRUS INFECTION IN THE YEAR 2009

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ABSTRACT

Background: *Dengue (DEN) virus, the most important arthropod-borne human pathogen, represents a serious public health threat. DEN virus is transmitted to humans by the bite of the domestic mosquito, Aedes aegypti, and circulates in nature as four distinct serological types DEN-1 to 4).* ***The aim of Study:*** *To identify Dengue Virus Serotype I which showed mild clinical performance in five years before and afterward showed severe clinical performance.* ***Material and Method:*** *Prospective and analytic observational study had been done in Dr. Soetomo Hospital and the ethical clearance was conduct on January 01, 2009. The population of this research is all cases of dengue virus infection. Diagnosis were done based on WHO 1997. All of these cases were examined for IgM & IgG anti Dengue Virus and then were followed by PCR examination to identify Dengue Virus serotype.* ***Result and Discussion:*** *DEN 2 was predominant virus serotype with produced a spectrum clinical illness from asymptomatic, mild illness to classic dengue fever (DF) to the most severe form of illness (DHF). But DEN 1 usually showed mild illness. Helen at al (2009–2010) epidemiologic study of Dengue Virus Infection in Health Centre Surabaya and Mother and Child Health Soerya Sidoarjo found many cases of Dengue Hemorrhagic Fever were caused by DEN 1 Genotype IV. Amor (2009) study in Dr. Soetomo Hospital found DEN 1 showed severe clinical performance of primary Dengue Virus Infection as Dengue Shock Syndrome two cases and one unusual case.* ***Conclusion:*** *The epidemiologic study of Dengue Virus Infection in Surabaya and Sidoarjo; in the year 2009 found changing predominant Dengue Virus Serotype from Dengue Virus II to Dengue Virus 1 Genotype IV which showed a severe clinical performance coincident with primary infection.*

Key words: *Changing Clinical Performance, Dengue Infection.*

INTRODUCTION

Dengue (DEN) virus, the most important arthropod-borne human pathogen, represents a serious public health threat. DEN virus is transmitted to humans by the bite of the domestic mosquito, Aedes aegypti, and circulates in nature as four distinct serological types DEN-1 to 4. DEN virus has been recognized in over 100 countries, and 2.5 billion people live in areas where DEN virus is endemic.[16]

Dengue, an emerging arboviral and arthropod borne disease, is a major cause of morbidity throughout the tropical and sub-tropical regions of the world.[1] Dengue virus (DV) infection with any 1 of 4 serotypes produces a spectrum of clinical illness, ranging from an asymptomatic or mild febrile illness to classic dengue fever (DF) to the most severe form of illness, dengue hemorrhagic fever (DHF). DHF is characterized by plasma leakage and a hemorrhagic diathesis near the time of differences, typically after 5 days of fever.[2] In severe DHF, morbidity and mortality are the result of hypotension and shock, at times accompanied by severe coagulation abnormalities and bleeding. Since early hospitalization and careful supportive care can reduce the case-fatality rate of DHF, the rapid identification of patients at risk for developing DHF is desirable in regions where DV is endemic.

Dengue hemorrhagic fever is one of the important health problem in Indonesia, although the mortality rate has been decreased but many dengue shock syndrome cases is very difficult to be solving handled. Natural course of dengue virus infection is very difficult to predict of the earlier time

of severity occur; It is may be due to the new variant of dengue virus that infect a child could be severe and can not be identified earlier.

Previous study show that some of DEN 2 and DEN 3 virus cases could show a clinical performance of severe dengue virus infection such as dengue shock syndrome.

Based on Halstead hypothesis, the severe dengue virus infection could be correlated with secondary infection. The infant cases show a severe clinical manifestation.

In Thailand and Cuba, many cases of dengue virus infection were identified as secondary infection and some of them showed dengue shock syndrome, but this case did not found in other countries. Moren (1980) found that the differences of growing dengue virus in monocyte could be a predictor of severity or mild cases for dengue virus infection.

The first outbreak of DHF in Indonesia was reported in Java Island in 1968, all types (Den VI-4) were isolated from patient in Jakarta in 1973–1974. Indonesia has approximately 100.000 annual dengue cases. Since then some outbreak in other cities and island were reported and the type of circulating DEN virus varies in each province and island. Based on Setiati TE et al (2006), recently predominant type as follow: Jakarta DEN V3; Palembang DEN V3; Bandung DEN V2; Manado DEN V1; Merauke DEN V3; Yogyakarta DEN V3.

In the year 2009, Dengue Virus Team of Institute Tropical Disease had done epidemiologic study in Surabaya.

MATERIAL & METHOD

Prospective and analytic observational study had been done in Dr. Soetomo Hospital and the ethical clearance was conduct on January 01, 2009. The population of this research is all cases of dengue virus infection that in Tropical ward of children, diagnosis were done based on WHO 1997. Cases of dengue virus infection were collected & involving in research based on inform concern. All of these cases were examined for IgM & IgG anti dengue virus and then followed by PCR examination to identify dengue virus serotype.

Blood examination should be done everyday. X-Ray examination were also done base on clinical performance of Pleural Effusion & Ascites. Data of all cases dengue virus infection should be analyze using method of Kruskal Walles & Mann Whitney and Regression Logistic multivariet.

RESULT & ANALYSIS

150 cases of primary and secondary of dengue virus infection were studied. Dengue virus was isolated from vero cell and 120 samples have positive CPE. 70 samples were found as serotype by doing RT-PCR examination.

Serotype DEN 1: there ware only 3 cases (see table 3) consisted of 2 cases had age 1-4 years and 1 had age 5–14 years. They showed a severe clinical performance as DSS 2 cases and 1 case as unusual case (see table 1).

Table 1. Distribution of Serotype and Clinical Performance of Dengue Virus Infection

	Clinical Performance & Diagnostic				
Serotype	**DF**	**DHF**	**DSS**	**UNUSUAL**	**Total**
DEN 1	0	0	2	1	3
DEN 2	30	26	7	2	65
DEN 3	1	0	1	0	2
DEN 4	0	0	0	0	0
Total	31	26	10	3	70

*Kruskal-Wallis: p = 0,03**

** = significant (p < 0,05)*

Table 2. Distribution of Clinical Performance of Dengue Virus Infection

	Clinical Performance & Diagnostic				
Type of Infection	**DF**	**DHF**	**DSS**	**UNUSUAL**	**Total**
Primary	16	7	1*	2	26
Secondary	15	19	9	1	44
Total	31	26	10	3	70

*Mann-Whitney; p = 0,035**

** = significant (p < 0,05)*

Serotype DEN 1 was usually mild case but in this study 1 case showed a severe clinical performance as DSS and identified as primary infection (see table2).

Table 3. Distribution of Primary and Secondary infection and Serotype that were correlated with clinical Performance of Dengue Virus Infection

	Clinical Performance & Diagnostic				
Type of Infection	**DF**	**DHF**	**DSS**	**UNUSUAL**	**Total**
Primary					
DEN 1	0	0	1*	0	1
DEN 2	16	7	0	2	25
DEN 3	0	0	0	0	0
DEN 4	0	0	0	0	0
Total	16	7	1	2	26
Secondary					
DEN 1	0	0	1	1	2
DEN 2	14	19	7	0	40
DEN 3	1	0	1	0	2
DEN 4	0	0	0	0	0
Total	15	13	9	1	44

The second case of DEN 1 was identified as secondary dengue virus infection and the third case was an unusual case which showed secondary of dengue virus infection (see table 3). Based on Yamanaka this serotype DEN 1 might be have genotype IV or mention as DEN 1 genotype IV.

DISCUSSION

Aryati (2005), Fedik (2007), had done an epidemiologic study of dengue hemorrhagic fever cases this in Surabaya, found that DEN virus 2 was a predominant types.

The study in Health Center of Surabaya DEN V2 was predominant in Surabaya (see table 4).

All of them showed clinical manifestation of dengue virus infection with produces a spectrum of clinical illness, ranging from an asymptomatic or mild febrile illness to classic dengue fever (DF) to the most severe form of illness as dengue hemorrhagic fever (DHF). DHF is characterized by plasma leakage and a hemorrhagic diathesis near the time of differences, typically after 5 days of fever (2). Most of them showed severe dengue hemorrhagic fever as the result of hypotension and shock, at the times accompanied by severe coagulation abnormalities and bleeding. Since early hospitalization and careful supportive care can reduce the case-fatality rate of DHF, the rapid identification of patients at risk for developing DHF is desirable in regions where DV is endemic. On the year 2007 13% (7 cases) showed very severe clinical performance of dengue virus infection due to combining virus of DEN 2 and DEN 3 infected in one host of dengue hemorrhagic fever case that could induce viremia.

But based on epidemiologic study in Surabaya & Sidoarjo on 2009 and 2010[27] found many cases of dengue hemorrhagic fever were caused by virus DEN V1 (see table 5).

The clinical performance of cases Dengue Virus Infection who came in health center of Surabaya in year 2008 with 2169 cases showed clinical performance of Dengue Fever 87% and 10% Dengue Hemorrhagic Fever and Dengue Shock Syndrome and 3% unusual manifestation. In the year 2009 with 2268 cases Dengue Virus Infection showed clinical performance of Dengue Fever 71.5% and Dengue Hemorrhagic Fever and Dengue Shock Syndrome 28% and unusual cases of Dengue Virus Infection 0.5% (see table 6).

This finding supported study of mosquito bites to some peoples live surrounding Dengue Hemorrhagic cases who had been admitted in hospital (see table 7).

Table 4. Prevelance Dengue Virus Infection based on serotype virus that was found in Surabaya on the year 2003–2005, 2007, 2008.

Year	DEN V1	DEN V2	DEN V3	DEN V4	D2+D3	Total
2003–2005	0	20 (80%)	4 (16%)	1 (4%)		25
2007	0	46 (87%)	0	0	13%	53
2008	0	20 (100%)	0	0		20

Table 5. Prevalence Dengue Virus Infection in Surabaya & Sidoarjo in 2009–2010.

Year	DEN V1	DEN V2	DEN V3	DEN V4	Total
2009	79 (87%)	6 (6.5%)	0	6 (6.5%)	91
2010 (Jan–Feb)	27 (100%)	0	0	0	27

Table 6. Clinical performance of dengue virus infection in Health Centre of Surabaya

Year	Total Patients	Dengue Fever	DHF + DSS	Unusual
2008	2169	1890 (87%)	216 (10%)	63 (3%)
2009	2268	1601 (71,5%)	656 (28%)	11 (0,5%)

Table 7. Virus Isolation from Mosquito

Mosquito	2008					
	Total	Pool	CPE	Immune staining	PCR	Sequencing
Ae.aegypti	271	12	2	Dengue	D2	D2
Cx.quinquefasciatus	336	10	4	Dengue	D2	D2
Cx.tritaeniorhynchus	131	3	–	–	–	–
Cx.vishnui	71	1	–	–	–	–
Cx.pseudovishnui	42	1	1	Dengue	D2	D2

Table 8. Virus Isolation from Mosquito

Mosquito	2009–2010					
	Total	Pool	CPE	Immune staining	PCR	Sequencing
Ae.aegypti	1784	45	13	Dengue	D1	D1
Cx.quinquefasciatus	74	4	1	Dengue	D1	

Table 7 supported previous epidemiologic study that found DEN V2 as predominant types in the year 2008 but table 8 supported epidemiologic study in the year 2009 found DEN V1 as predominant types. The study in Dr. Soetomo hospital since January 1, 2009 as followed DEN 1 showed clinical performance of Dengue Shock Syndrome 2 cases and unusual case with total 3 cases, DEN 2 were found clinical performance of 30 cases Dengue Fever, 26 Dengue Hemorrhagic Fever 7 Dengue Shock Syndrome and 2 unusual cases, with total 65 cases. DEN 3 were found clinical performance of Dengue Fever 1 case Dengue Shock Syndrome 1 case, with total 2 cases. Den 4 virus was not found. The differences of result were found due to the differences of population of study. But DEN V1 were always found in this study.[27]

Virus isolation from mosquito bites showed DEN V1 has been isolated and identified on DEN 1 Genotype IV, it was new variant virus that correlated with phylogenetic Dengue Virus came from Beijing which had severe clinical performance of Dengue Virus Infection.

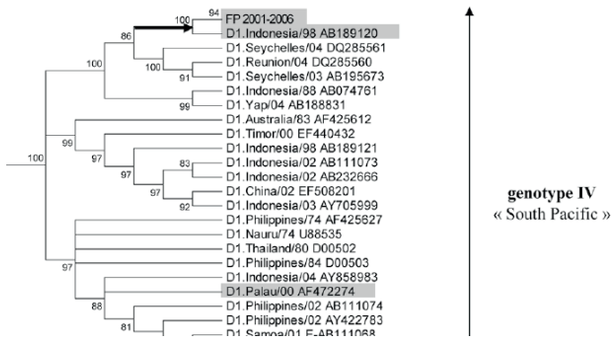

Figure 1. Phylogenetic Dengue Virus in The World

In the year 2009 we have many experience to care severe performance of Dengue Virus Infection with unusual manifestation that could not followed WHO criteria 1997. More cases showed criteria for severe dengue virus infection, as followed: Severe plasma leakage (leading to: shock/DSS, Fluid accumulation with respiratory distress), Severe bleeding (as evaluated by clinician), Severe organ involvement (Liver: AST or ALT > = 1000, CNS: Impaired consciousness, Heart and other organ). Therefore for managing the unusual dengue virus infection we should followed new WHO criteria diagnosis and classification of cases as followed.

During three decades, the World Health Organization (WHO) has recognized and recommended the classification of dengue in: dengue fever (DF) and dengue hemorrhagic

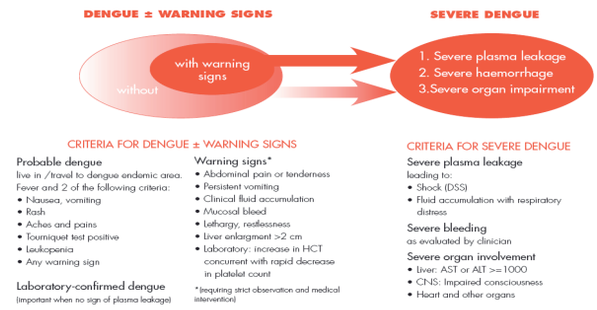

Figure 2. Suggested dengue case classification and levels of severity. Dengue guidelines for diagnosis, treatment, prevention, and control. World Health Organization, UNICEF, UNDP. New Edition 2009

fever (DHF) with or without dengue shock syndrome (DSS).[6] However in some severe cases the clinical manifestations sometimes doesn't fit to these definition and classification. In this WHO recommendation clinical manifestation in DF are mild form than DHF/DSS, but in this case DF with severe hemorrhagic manifestation and that may be life threatening. Dengue can also express itself by means of the so-called "atypical" forms or unusual manifestation.[1,5] These unusual clinical manifestations may delay recognition of potentially severe disease.

Lately, several publications that appeared worldwide emphasize the need to revise the classification of severe dengue.[1] One of the revised dengue classification proposed by DENCO (Dengue Control) has been applied and studied in several countries in Asia and Latin America with good result.[1,7] The DENCO study concluded that 18 to 40% of the cases could not be classified by means of the current WHO Classification, and over 15% of unusual cases with shock could not be classified as severe cases of dengue either, since they did comply with some of the criteria to be regarded as a case of DHF/DSS.[1,7]

The pathogenesis of bleeding in DF is poorly understood. Thrombocytopenia may enhance the risk, but the primary cause of bleeding is unknown. Limited data suggest that activation of coagulation and fibrinolysis play role in the pathogenesis (srichaikul). An imbalance in the regulation of coagulation and fibrinolysis, as in disseminated intravascular coagulation syndrome (DIC), in conjunction with the characteristic thrombocytopenia may contribute to the bleeding tendency in DF.

In the year 2009, the study found that DEN V1 genotype IV showed a severe clinical performance. Of a primary dengue virus infection. This study supported to Gubler

hypothesis which gave information that a new virulent variant DEN V1 can cause a severe clinical performance of dengue virus infection.

SUMMARY

The epidemiologic study of Dengue Virus infection in Surabaya. In the year 2009 found a changing predominant Dengue Virus from Dengue Virus 2 to Dengue Virus 1 genotype 4 which showed a severe clinical performance coincident with primary infection.

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