Clinical and virological profile of Dengue cases: a study in Samarinda and Manado

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Abstrak

Latar Belakang: *Infeksi virus dengue masih merupakan masalah kesehatan di Indonesia. Studi ini dilakukan di Samarinda dan Manado, tujuannya untuk mendapatkan profil klinis dan virologi dari penderita anak dan dewasa di Wilayah Tengah Indonesia.*

Metode: *Ini merupakan studi deskriptif, kasus infeksi dengue didapat dari Rumah Sakit Umum di Samarinda dan Manado pada tahun 2012-2013. Sampel darah berasal dari penderita infeksi dengue yang dirawat di Bagian Anak dan Penyakit Dalam. Konfirmasi infeksi dengue dilakukan dengan pemeriksaan nested RT-PCR, deteksi antibodi Ig M dan Ig G dilakukan dengan capture ELISA untuk menentukan kemungkian infeksi dengue maupun jenis infeksi. Definisi infeksi primer dan sekunder berdasarkan keberadaan antibodi Ig G. Profil klinis dijabarkan berdasarkan sampel terkonfirmasi infeksi dengue.*

Hasil: *Sebanyak 485 penderita ikut dalam penelitian ini, 40 % diantaranya terkonfirmasi infeksi dengue. Tiga puluh lima persen diantaranya kemungkinan terinfeksi virus dengue berdasarkan antibodi. Secara umum virus dengue serotipe 2 (DENV-2) paling banyak ditemukan pada penelitian ini, selain itu ditemukan juga infeksi campuran (2 serotip berbeda) di Samarinda. Sebanyak 72 % dari kasus terkonfirmasi infeksi dengue merupakan infeksi sekunder, demikian juga pada penderita anak. Demam, sakit kepala, mual dan nyeri pada perut merupakan profil klinis yang paling banyak ditemukan.*

Kesimpulan: *Keempat serotip virus dengue ditemukan dari kasus-kasus di RS Abdul Wahab Sjahranie, Samarinda dan RS. Prof. Dr. R.D. Kandou, Manado, secara umum DENV-2 merupakan yang paling dominan. Kebanyakan penderita sudah pernah terinfeksi dengue sebelumnya demikian juga penderita anak.* ***(Health Science Journal of Indonesia 2018;9(2):76-81)***

Kata kunci: *Infeksi dengue, Samarinda, Manado*

Abstract

Background: Dengue infection is one of public health problem in Indonesia. This study was conducted Samarinda and Manado, which aimed to report of clinical and virological profile among hospitalized children and adult dengue patients in central region of Indonesia.

Method: This was a descriptive study, dengue cases were collected in general hospital in Samarinda and Manado from 2012 to 2013. Patient with dengue infection when admitted from pediatric and internal diseases ward included in this study. Sera were collected and nested RT-PCR was performed to confirmed dengue virus. Dengue Ig M/Ig G antibodies detected using capture ELISA for probability of dengue infection. Definition of primary and secondary infection was based on existence of IgG antibodies. Clinical profile was described base on confirmed results.

Results: Four hundred and eighty five cases were included; 40 % were confirmed dengue infection and 35 % were probably dengue infection based on antibody. Dengue serotype 2 was dominant from both sites, furthermore mixed infections were found in Samarinda. Seventy two percent of confirmed cases were secondary infection, likewise in children. Fever, headache, nausea and abdominal pain were the most common signs and symptoms of confirmed cases.

Conclusion: All four serotype of DENV found cases in Abdul Wahab Sjahranie Hospital, Samarinda and Prof. Dr. R.D. Kandou Hospital, Manado, generally DENV-2 were dominant. Most of the cases have been exposed to dengue infection previously similarly in children. ***(Health Science Journal of Indonesia 2018;9(2):76-81)***

Key words: Dengue infection, Samarinda, Manado

Dengue viral infection is a major public health consequence in tropical and subtropical countries. WHO estimates half of world's population lives in dengue endemic countries.[1] Indonesia territory is in the dengue endemic zone. Dengue cases were report firstly in Jakarta and Surabaya in 1968[2] and spread out to other cities. Currently dengue cases are epidemic in capital cities of all provinces.[3]

Dengue virus (DENV) is grouped in family *Flaviviridae* and genus *Flavivirus*, and is transmitted by *Aedes aegypti* mosquitoes.[4] Clinical manifestation of DENV infection ranges from asymptomatic to severe illness and may lead to fatality.[5] Four serotype of DENV spread throughout Indonesia, and DENV-3 was reported dominant.[3] Dengue virus serotype associated with severe disease [6] while secondary infection with different serotype of previous infection provoked severe clinical manifestation.[5]

Information of dengue serotypes in Indonesia was still limited, especially in central Indonesia. This study aims to report of clinical and virological profile among hospitalized children and adult patients in Samarinda and Manado as capital cities in central Indonesia.

METHODS

Study Population

This was a descriptive study of dengue disease in two general hospitals in Samarinda and Manado. The data were collected between April to December 2012 in Manado, September 2012 to April 2013 in Samarinda. The hospitals were Abdul Wahab Sjahranie General Hospital in Samarinda and Prof. Dr. R.D Kandou General Hospital in Manado Cities.

The study were conducted at pedriatic and internal medicine departments of both hospitals, with dengue infection was diagnosed when admitted. Age criteria of pedriatic wards of both hospitals were ≤12 years old, and > 12 yo for adults. Patients should have at least 2 of the following dengue-associated signs or symptoms: positive tourniquet test, manifestation of haemorrhage (eg, petechiae, ecchymosis, purpura, hematemesis and melena or other bleeding), thrombocytopenia (thrombocyte less than 100,000/mm$^{3)}$ and signs of plasma leakage (eg, hemoconcentration, ascites, pleural effusion and hypoproteinemia).[7] The patients were progressively followed during hospitalization and clinical manifestations were recorded in a questionnaires.

Laboratory Assessments

Sera from one to two cc patient's acute blood samples were collected to performed nested RT-PCR (Lanciotti *et al* method) [8] for virus detection and confirmation of dengue infection. Detection of dengue IgM and IgG were also performed using commercial dengue IgM and IgG capture ELISA (Panbio). It was set to detect high level of IgG antibody of dengue infection to distinguished with primary infection. In initial phase of disease IgG antibody is detectable at high level.[7]

Definitions

Confirmed dengue virus infection; RNA viral were detected in sera acute samples whereas probable cases were positive dengue IgM or IgG. In this study, primary infection was defined as confirmed dengue virus infection result in which IgM negative or positive and IgG negative. Secondary dengue virus infection defined as a confirmed dengue virus infection in which dengue IgG antibodies were detected. Severity of dengue infection were analyzed using WHO classification.[7]

Ethical Consideration

This study was approved by National Institute of Health Research and Development Ethics Committee, number KE.01.05/EC/402/2012. All cases were analyzed with anonymously and informed consent was obtained from all patients upon enrollment.

RESULTS

A total of 485 blood samples of suspected dengue cases were collected from AW Sjahranie General Hospital in Samarinda and Prof R.D Kandou General Hospital in Manado Cities. Two hundred and fifty-eight cases were obtained from AW Sjahranie Hospital and 227 cases from Kandou Hospital.

Blood samples were collected after obtaining informed consent from patients. The samples were used for dengue virus and antibody detections. Table 1 demonstrated virus confirmation and serology results of this study. Of all samples tested, 194 (40%) were confirmed dengue infection, while 171 (35%) were probable based on antibody detection.

Table 1. Laboratory confirmation of dengue cases

	Confirmation*			Total
	Confirmed	*Probable*	*Not Confirmed*	
Manado	109	91	27	**227**
Children (≤12 yo)	85	66	15	166
Adults	24	25	12	61
Samarinda	85	80	93	**258**
Children (≤12 yo)	17	17	5	39
Adults	68	63	88	219

*No of cases

Nested RT-PCR was conducted to obtain dengue virus serotype. All serotypes of DENV were found in Samarinda and Manado Cities. Among all cases, DENV-2 was the predominant serotype followed by DENV-3 and DENV-1. In Manado we only found single DENV infection, but in Samarinda City we also found mixed infections. (Table 2). Serotype 2 and 3 were more found in mixed infections than other serotypes.

Monthly distribution of dengue serotypes in Manado City show in figure 1, which indicate almost all of serotypes were found in each month. Different distribution of Dengue serotypes were found in Samarinda City (figure 2), complete serotypes and mixed infections were found in January to March.

Table 3 shows the characteristics of confirmed cases. Children were the most confirmed cases from Manado, while adult patients were from Samarinda (real situation). The majority of confirmed dengue patients were >8-12 years in Manado City, slightly different between >12-19 years and 25+ years in Samarinda City. Males were more than females of the confirmed dengue cases.

Table 2. Dengue serotype

	Serotype				*Mixed*			
	DENV-1	DENV-2	DENV-3	DENV-4	*DENV-1+2*	*DENV-2+3*	*DENV-3+4*	*DENV-2+4*
Manado (n= 109)	32	44	26	7				
Samarinda (n=85)	15	24	22	11	4	7	1	1

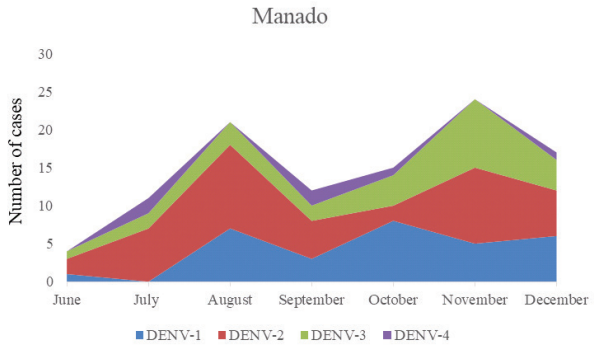

Figure 1. Monthly distribution of dengue serotype in Manado 2012

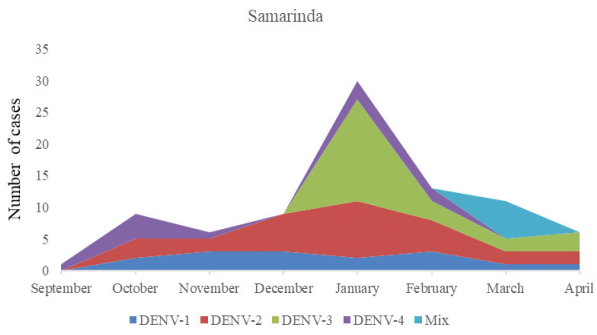

Figure 2. Monthly distribution of dengue serotype in Samarinda 2012-2013

Table 3. Characteristic of confirmed of dengue cases (N=194)

	No. of cases (%)	Age						Sex	
		0-<5	5-8	>8-12	>12-19	20-24	25+	Male	Female
Samarinda	85	6	7	10	23	15	24	59	26
Children (%) (≤12 yo)	17(20)								
Adults (%)	68(80)								
Manado	109	20	24	38	15	5	7	60	49
Children (%) (≤12 yo)	85(78)								
Adults (%)	24 (22)								

Type of infection and severity of dengue cases are shown in table 4. Distributions of primary and secondary infections from both hospitals were similar. Most of confirmed samples were secondary infection (74.2%). This study also found majority diagnosed with dengue fever. In Samarinda 56% of adult were diagnosed dengue fever, 44 % were dengue hemorrhagic fever grade II. While 44% children were diagnosed dengue fever and 43% were dengue hemorrhagic fever grade I in Manado.

Table 4. Clinical aspect of confirmed cases (N=194)

	Type of infection		Severity of disease		
	Primary	Secondary	DF	DHF I	DHF II
Samarinda	**33**	**52**	**48**	**1**	**36**
Children (N=17) (≤12 yo)	4	13	10	1	6
Adults (N=68)	29	39	38	0	30
Manado	**35**	**74**	**47**	**41**	**21**
Children (N=85) (≤12 yo)	27	58	38	37	10
Adults (N=24)	8	16	9	4	11

*Number of cases DF : Dengue Fever
DHF I : Dengue hemorrhagic fever grade I
DHF II: Dengue hemorrhagic fever grade II

Table 5 shows the distribution of clinical characteristic observed in this study. Fever, headache, nausea and abdominal pain were the common signs and symptoms of confirmed cases when patients came for admission. Signs and symptoms between children and adults were slightly different, especially retroorbital, muscle and abdominal pain.

DISCUSSION

Here we show the profile of virological and clinical dengue cases in Samarinda and Manado Cities. During period of study sera were collected of 485 patients in both area. Of all sera 40% were confirmed and 35% were probable of dengue infection. Confirmed cases were defined by detection of DENV nucleic acid by RT-PCR. Dengue virus nucleic acid can be detected within four to seven days of illness.[9]

Table 5. Sign and symptoms of confirmed cases

Symptom	Children (N= 102) No of cases (%)	Adults (N= 92) No of cases (%)
Fever	102 (100)	92 (100)
Headache	35 (34)	79 (86)
Retroorbital pain	2 (2)	34 (37)
Muscle pain	4 (4)	46 (50)
Joint pain	2 (2)	48 (52)
Nausea	32 (31)	73 (79)
Abdominal pain	34 (33)	52 (56)
Vomiting	43 (42)	35 (38)
Spontaneous bleeding	8 (8)	21 (23)
Rash	9 (9)	23 (25)
Rhonchi	5 (5)	0
Hepatomegaly	27 (27)	4 (4)
Splenomegaly	5 (5)	0
Ascites	1 (1)	0
Petechiae	11 (11)	32 (35)
Rumple Leed test	22 (22)	3 (3)

Probable cases were defined by detection of anti-DENV antibodies by IgM capture ELISA. We only had single blood sample and it's known that positive result of IgM antibodies do not necessarily mean is current infection, because of the persistence of IgM antibodies for several months and the patients might be had dengue infection in previous two or three months.[9] We also used Panbio dengue IgG capture ELISA (Brisbane, Australia) to detect dengue Ig G antibodies of the samples. The kit is set to detect higher level of specific dengue IgG antibodies, high IgG level indicates of secondary infections (Product brochure). IgG positive in single sample with greater titre indicate dengue infection.[9] In this study twenty five percent of these samples were unknown and could not confirmed using NS1 kit.

All serotype of DENV were found at these hospitals, but serotypes distribution were different. DENV-2 was dominant in Samarinda dan Manado. DENV-1 was more frequent in Manado than in Samarinda. Mixed infections were detected in Samarinda,

which indicates hyperendemic and high burden of disease in the city.[10] Mixed infection or serotype co-infections have been widely reported.[11,12,13] Since more than one serotype could be present in a single larva[14] it was possible to found serotype co-infection in dengue cases. Some studies also reported that different serotypes caused distinct effects upon the severity of dengue virus infections [6,15,16] and are worthy consideration when making clinical prediction upon dengue virus infection.[17] We have found predominance of DENV-2 both in single infections and mixed infection among patients admitted to major hospital in Samarinda and Manado.

In Samarinda confirmed cases increased in January to March, in line with other study in Samarinda that dengue cases increased in December to May.[18] Monthly distribution of dengue serotypes in Samarinda and Manado describe predominant serotypes throughout the study period. All serotypes found in each month during the study. While complete serotypes and mixed infection found in January to March in Samarinda along with an increase in number of cases. (Figure 1 and 2). Another study reported that dengue virus serotypes can be replaced quickly and developed into outbreaks,[19] virological surveillance required for early detection.

Most of suspected cases in Manado were children and were adult in Samarinda. Compared to other report, most of suspected cases in Samarinda 2007-2008 were adults.[18] Our data shows that male more than female from both cities, it also accordance with other studies.[20,21,22]

Secondary infection defined by detection of dengue IgG antibodies and primary infection defined by no dengue IgG antibodies detected of confirmed dengue.[9] We found majority of confirmed cases were secondary infection. Even 70% of children which dengue confirmed were secondary infection. Even though severity of disease were mild to moderate. Severity of diseases defined by WHO classification.[9] Souza D *et al* reproted that adults have more severe form of disease relative than children.[23] This study also shows that adults exhibited a higher frequency of dengue hemorrhagic fever grade II than children. Secondary infection was not associated with diseases severity.[24] Although dengue hemorrhagic fever (grade I and II) cases more than dengue fever, no DSS (dengue shock syndrome) in our study. Other study reported that serotype co-infection had severe desease,[12] but another reported that it not necessarily cause more severe disease.[11] In our study 69% of mixed infection had dengue fever.

All of confirmed dengue cases had fever when admitted to hospital. Most of adult patients presented with headache, nausea and abdominal pain when admitted, while vomiting, nausea and abdominal pain are more presented in children. It might be due to children is less able to determine of certain pain. Generally clinical featured in this study consistent with other report.[25]

In conclusion, we have presented the profile of dengue cases of two hospitals in Samarinda and Manado. Most of the cases have previously been exposed to dengue infection likewise in children. All serotypes of DENV were found in Abdul Wahab Sjahranie Hospital, Samarinda and Prof. Dr. R.D. Kandou Hospital, Manado, generally DENV-2 were dominant in both cities.

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