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Research Report

# FEVER AS INDICATOR TO SECONDARY INFECTION IN DENGUE VIRAL INFECTION

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***ABSTRACT***

*Dengue Virus Infections are distributed in tropical and sub-tropical regions and transmitted by the mosquitoes such as Aedes aegypti and Aedes albopictus. Dengue virus can cause dengue fever, dengue hemorrhagic fever and dengue shock syndrome or dengue and severe dengue classified by World Health Organization. Beside it concurrent infection virus salmonella had been found some cases who showed fever more than 7 days. Concurrent infection with two agents can result in an illness having overlapping symptoms creating a diagnostic dilemma for treating physician, such as dengue fever with typhoid fever. The aim of this research is detection of dengue virus and secondary infection with Salmonella typhi in patients suspected dengue virus infection. Detection of dengue virus and Salmonella typhi using immunochromatography test such as NS1, IgG/IgM for dengue virus infection, and IgM/IgG Salmonella and blood culture. The fifty children with dengue virus infection came to Soerya hospital and 17 cases suspected dengue virus infection, five cases showed a positive NS1 on the second day of fever and one case concurrent with clinical manifestation of convulsi on the third days of fever there were five cases only showed positive. It was showed in this study that on the fourth to six day of fever in dengue virus infection accompanied by antibody IgM & IgG dengue. There were 12 cases showed the clinical manifestation of concurrent dengue viral infection and Salmonella, all of them showed a mild clinical manifestation and did not show plasma leakage and shock. In this study we found the length of stay of concurrent Dengue Virus Infection and Salmonella infection is more than 10 days. These patients were also more likely to have co-existing haemodynamic disturbances and bacterial septicaemia which would have required treatment with inotropes and antibiotics. This idea is very important to make update dengue viral management to decrease mortality in outbreak try to gain new prevention method before the occurrence of outbreak.*

***Keywords:*** *dengue viral, Salmonella typhi, co-infection, secondary infection, laboratory test*

***ABSTRAK***

*Infeksi Virus Dengue didistribusikan di daerah tropis dan sub-tropis dan ditularkan oleh nyamuk seperti Aedes aegypti dan Aedes albopictus. Virus dengue dapat menyebabkan demam berdarah, demam berdarah dengue dan sindrom syok dengue atau demam berdarah dan demam berdarah parah yang dikelompokkan oleh Organisasi Kesehatan Dunia. Disamping itu infeksi sekunder oleh Salmonella telah ditemukan beberapa kasus yang menunjukkan demam lebih dari 7 hari. Infeksi bersama dengan dua agen dapat menyebabkan penyakit yang memiliki gejala tumpang tindih yang menciptakan dilema diagnostik untuk pengobatan, seperti demam berdarah dengan demam tifoid. Tujuan dari penelitian ini adalah deteksi virus dengue dan infeksi sekunder dengan Salmonella typhi pada pasien yang diduga terinfeksi virus dengue. Deteksi virus dengue dan Salmonella typhi menggunakan uji imunokromatografi seperti NS1, IgG/IgM untuk infeksi virus dengue, dan IgM/IgG Salmonella dan kultur darah. Lima puluh anak dengan infeksi virus dengue datang ke rumah sakit Soerya dan 17 kasus yang diduga terinfeksi virus dengue, lima kasus menunjukkan NS1 positif pada hari kedua demam dan satu kasus bersamaan dengan manifestasi klinis konvulsi pada hari ketiga demam terjadi lima kasus. Hal ini ditunjukkan dalam penelitian ini bahwa pada demam dengue keempat sampai enam hari disertai dengan antibodi IgM dan IgG. Ada 12 kasus yang menunjukkan manifestasi klinis infeksi virus dengue bersamaan dan Salmonella, semuanya menunjukkan manifestasi klinis ringan dan tidak menunjukkan kebocoran dan kejutan plasma. Dalam penelitian ini kami menemukan lamanya tinggal bersamaan Infeksi Dengue Virus dan infeksi Salmonella lebih dari 10 hari. Pasien-pasien ini juga cenderung memiliki gangguan hemodinamik yang*

*menyertai dan bakteri septicemia yang memerlukan pengobatan dengan inotrop dan antibiotik. Ide ini sangat penting untuk membuat update manajemen virus dengue untuk menurunkan angka kematian saat wabah dan mencoba mendapatkan metode pencegahan baru sebelum terjadinya wabah.*

***Kata kunci:*** *virus dengue, Salmonella typhi, koinfeksi, infeksi sekunder, uji laboratorium*

## INTRODUCTION

Dengue Virus Infections are distributed in tropical and sub-tropical regions and transmitted by the mosquitoes such as *Aedes aegypti* and *Aedes albopictus*.[1–3] Dengue virus can cause dengue fever, dengue hemorrhagic fever and dengue shock syndrome or dengue and severe dengue classified by World Health Organization.[4]

The patient came to the doctor in first, second, third days of fever or more days fever than following by other clinical manifestation such as Salmonella infection some other bacterial infection and virus. Based on clinical manifestation some laboratory test that should be done such as (1); For dengue viral infection: NS1, IgM & IgG[5] (2); For Salmonella infection: IgM IgG Salmonella[6] (3); culture of blood for looking other bacterial infection. Based on these information the doctor should be aware to care and prevent to dengue virus infection.

The pathogenic mechanism of DHF has not been fully elucidated, but it is generally accepted that disease severity is related to viremia level. Antibody-dependent enhancement (ADE) of infection is a hypothetical mechanism that possibly leads to increased viremia levels. A major factor in ADE is the cross-reactive non-neutralizing antibodies induced by a former (primary) infection. These can enhance DENV infection in monocytes/Macrophages in an Fc gamma receptor (FcyR)- medicated manner upon secondary exposure to a heterotypic infection, thus they are called 'enhancing anti bodies'.[7] In contrast, neutralizing antibodies can decrease viremia levels and are considered to play a protective role against infection. Under in vivo conditions, the enhancing and neutralizing antibody species are present in the circulation as polyclonals. Therefore, the total activity, namely the balance of these two opposing activities, is a potentially critical factor determining viremia level and disease outcomes.[8]

Our present sero-epidemiological study is aimed to investigate dengue antibody status in endemic children. We used serum samples collected from healthy Philippine children in 1993 and from a population of Indonesia children between 1999 and 2000. We are measured the balance of enhancing and neutralizing activities against search DENV type at varying serum dilutions in the presence or absence of complement. A variety of dose (serum dilution)-dependent antibody activity patterns were observed among the children. In the present study is revealed that most infected children possessed enhancing antibodies against one or more the DENV types at a serum dilution of 1:10.[8] Importantly, enhancing activity was not reduced by the addition of complement in our in vitro assay condition.

Concurrent infection with two agents can result in an illness having overlapping symptoms creating a diagnostic dilemma for treating physician, such as dengue fever with typhoid fever. The similarity in symptoms and differential diagnoses of these diseases often mimic those of dengue and thereby makes accurate clinical diagnosis and treatment difficult without laboratory confirmation. Some laboratory test was taken more of NS1, IgM dengue to identify for viral infection.[9,10] IgM/IgG Salmonella and blood culture to identify for Salmonella infection.[11,12] This idea is very important to make update dengue viral management to decrease mortality in outbreak try to gain new prevention method before the occurrence of outbreak.

## MATERIAL AND METHOD

Since 1st January until 30th April 2017, there were 50 children with dengue virus infection came to Soerya mother and child hospital and 17 cases suspected dengue virus infection who came late. All of them were coming to doctor due illness feeling and showed the clinical manifestation such as fever, headache, vomiting, and tired and following by diarrhea, colic abdomen, and cough. To complete the data, the laboratory test such as NS1 kit by SD Bioline (US), IgM & IgG dengue for dengue virus infection identification by SD Bioline (US), IgM/IgG Salmonella by SD Bioline (US) and blood culture for Salmonella infection identification.

## RESULT AND DISCUSSION

There were 17 cases came early to the hospital due to the clinical manifestation of high fever and one until three cases suffer from convulsion. All of them were examined physically and were done NS1, IgM and IgG dengue test to identify dengue viral infection. One case is showed a positive NS1. It was a case with clinical manifestation of fever more the 39°C with convulsion on the first day.

Five cases are showed a positive NS1 on the second day of fever and one case concurrent with clinical manifestation of convulsion on the third days of fever. There were five cases which only showed positive, the study is showed Table 1 fever with test of positive NS1. Clinical manifestation in patient of suspected dengue virus infection with NS1 positive such as fever, nausea, vomiting, abdominal pain, diarrhea, plasma leakage and epistaxis.

Two groups of cases are suspected Dengue Virus Infection had been made, as: 1) who had come on the

first, second, and third of fever as shown in Table 1 and 2) who had come on the fourth, fifth, and sixth of fever as shown in Table 2. NS1 test had been done in the first group cases of Dengue Virus Infection and the result showed on Table 1.

Seven cases who had a negative result NS1 had been followed by of IgM test on the four until six day of fever. The result see Table 2. It is showed in this study that on the fourth to six day of fever in dengue virus infection accompanied by antibody IgM & IgG dengue as shown in Table 2 and 3. There were 5 cases who had shown a clinical manifestation on the fourth, fifth, and sixth days of fever and had been identified as a positive result of IgM test. These event were also found of the following 5 cases that had a clinical manifestation on the third days of fever. Clinical manifestation in patient of suspected dengue virus infection with IgM positive such as fever, nausea, vomiting, and abdominal pain.

Seven cases who had a negative result NS1 had been be followed by of IgG & IgM test on the four until six day of fever. The results as shown in Table 2. It was showed in this study that on the fourth to six day of fever in dengue virus infection usually accompanied by antibody to viral of dengue as shown in Table 2 and 3.

On the Table 4 there were 12 cases showed the clinical manifestation of concurrent dengue viral infection and Salmonella. There were 12 cases positive only IgM, it mean that all cases has been suffered from primary infection of dengue virus. All of them are showed a mild clinical manifestation and did not show plasma leakage and shock. Two were cases showed a positive IgG and 12 cases were showed a positive IgM and IgG. It mean that all cases had been suffered from secondary infection dengue. These cases are showed severity of clinical manifestation of Dengue Haemorrhagic Fever. It was due to enhancement Ag Ab reaction that promoting the inclination of plasma leakage and shock.

Dengue fever manifests as spectrum of illness ranging from in apparent or mild febrile illness to serve and fatal hemorrhagic disease. In a typical case of dengue fever, the patient experiences high fever lasting for 5 to 7 days. Concomitantly, a severe frontal and retro orbital headache, myalgias, especially lower back, arm, and leg pains, malaise, arthralgia and anorexia. In typhoid fever, a dull continuous frontal headache begins during the first two days of fever, mild arthralgia involving multiple joints and vague, poorly localized back pain may occur.[13] In the previous study, risk factors for bacterial co-infection in children with dengue have not been well characterized. In a study done in adult patients, prolonged fever (> 5 days) was an independent risk factor for co-infection. The reasons for bacterial co-infections in some patients with dengue virus can cause a diminished T cell proliferation in response to mitogens *in vitro*. However, the *in vivo* effects of these observations have not been studied.[14] On 2017 there were

**Table 1.** NS1 test result in suspected dengue virus infection before three days in Soerya Hospital Sepanjang

| Day of Fever | NS1 Test Examination | | Total Cases |
|---|---|---|---|
| | + | - | |
| First day | 0 | 1 | 1 |
| Second day | 5 | 3 | 8 |
| Third day | 5 | 3 | 8 |
| Total cases | 10 | 7 | 17 |

**Table 2.** IgM, IgG, IgM & IgG rapid test followed negative test NS1

| Day of Fever | NS1 Test Examination | | | Total Cases |
|---|---|---|---|---|
| | IgM (+) | IgG (-) | IgM & IgG (+) | |
| Fourth | 1 | 0 | 2 | 3 |
| Fifth | 3 | 0 | 0 | 3 |
| Sixth | 1 | 0 | 0 | 1 |
| Total | 5 | 0 | 2 | 7 |

**Table 3.** Patient's IgM, IgG, IgM & IgG rapid test for identification dengue virus infection come in day 4th until day 7th

| Day of Fever | NS1 Test Examination | | | Total Cases |
|---|---|---|---|---|
| | IgM | IgG | IgM & IgG | |
| Fourth | 8 | 2 | 6 | 16 |
| Fifth | 6 | 0 | 3 | 9 |
| sixth | 2 | 0 | 2 | 4 |
| Seven | 3 | 0 | 1 | 4 |
| Total | 19 | 2 | 12 | 33 |

**Table 4.** The clinical manifestation of concurrent dengue virus infection and Salmonella

| Symptoms | Dengue Virus Infection | | Dengue Virus Infection+Salmonella | |
|---|---|---|---|---|
| Fever | 100% | 30 | 100% | 12 |
| Nausea | 62% | 18 | 83% | 10 |
| Vomiting | 40% | 12 | 60% | 7 |
| Diarrhea | 6% | 2 | 20% | 2 |
| Abdominal pain | 34% | 10 | 71% | 8 |
| Plasma leakage | 2% | 1 | 10% | 1 |
| Epistaxis | 2% | 1 | - | - |

found 12 cases of concurrent Dengue Virus Infection and Salmonella. In this study we are found the length of stay of concurrent Dengue Virus Infection and Salmonella infection is more than 10 days. These patients were also more likely to have co-existing haemodynamic disturbances and bacterial septicaemia which would have required treatment with inotropes and antibiotics. Furthermore, older patients would have other co-morbidities and have rehabilitation issues which may complicate admissions and extend hospital stay.[15] In November 2008 the predominant serotype from DENV Type 2 (DENV-2) to DENV type 1 (DENV-1) had been found,[16–18] July 2013 the predominant of DENV-1 to DENV-2 and the predominance of DENV-2 continued in 2014. All DENV-2 which isolated in Surabaya were classified into the cosmopolitan genotype, and further divided into 6 clusters defined as the "Surabaya Lineage".[19] In previous study was reported that genome sequence of DENV-1, which is phylogenetic close to the Japanese outbreak strain of 2014. This finding is indicated that the Southeast Asian region was the source of the dengue outbreak in Japan 2014. This abstract based on the reviewed of some studies that had been done in 2008-2014.[20,21]

Based on this result the monitoring of emergence imported or mutated strain of Dengue Virus in human being and mosquito emergence should be done. Therefore continuous surveillance of circulating viruses is required to predict the risk of DHF and DF.

This idea is very important to make update dengue viral management to decrease mortality in in outbreak try to gain new prevention method before the occurrence of outbreak.

## CONCLUSION

Monitoring clinical manifestation should always be done, to predict the appropriate diagnosis of Dengue Virus Infection. And Sero-epidemiology study should be continued doing in many the capital city of island in Indonesia.

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