

LIVER INVOLVEMENT IN CHILDREN WITH DENGUE INFECTION

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ABSTRAK

Hati bukanlah organ target utama virus dengue, meskipun disfungsi hati telah dilaporkan pada pasien dewasa dengan infeksi dengue. Hanya sedikit penelitian kasus gangguan hati pada anak dengan infeksi dengue. Penelitian ini adalah untuk mengetahui manifestasi dari keterlibatan hati pada anak dengan infeksi dengue. Penelitian ini merupakan studi kasus-kontrol dilakukan di RSUD Dr. Soetomo dari Maret 2008 sampai April 2009. Subjek penelitian adalah anak penderita infeksi virus dengue dengan diagnosis klinis berdasarkan kriteria WHO. Data diambil dari rekam medis. Variabel yang diteliti terdiri dari usia, jenis kelamin, manifestasi klinis termasuk hepatomegali, jaundice, ensefalopati, gangguan peredaran darah, serta temuan laboratorium, termasuk aspartate aminotransferase serum (AST) dan alanine aminotransferase (ALT). Data dianalisis menggunakan chi-square dan t-test dengan tingkat kepercayaan 95%. Ditemukan bahwa dari 72 pasien, 34 pasien mengalami hepatomegali, 4 pasien mengalami ensefalopati hati, dan 52 pasien dengan tingkat transaminase serum meningkat. Ada perbedaan yang signifikan dalam peningkatan tingkat AST (perbedaan mean 28,5 [9,4-47,5], p 0,004) dan hepatomegali (proporsi perbedaan 0,3 [0,1 sampai 0,5], p 0,018) berhubungan dengan keparahan. ALT tingkat yang lebih tinggi > 3 kali lipat (PR 4.1, 1,4-11,9, p 0,008) dan hepatomegali (PR 3,5, 1,2-10,1, p 0,018) dikaitkan dengan kegagalan peredaran darah. Dalam kesimpulan, manifestasi keterlibatan hati pada anak dengan infeksi dengue dalam penelitian ini adalah hepatomegali, peningkatan serum transaminase tingkat, dan ensefalopati hati. Peningkatan tingkat ALT > 3 kali lipat dan hepatomegali terkait dengan kegagalan sirkulasi.

ABSTRACT

Liver is not the major target organ of dengue virus, otherwise hepatic dysfunction has been reported in adult patient with dengue infection. Only a few cases of liver involvement in children with dengue infection have been explored. This study was to investigate manifestations of liver involvement in children with dengue infection. This was a case-control study was conducted at dr. Soetomo Hospital from March 2008 to April 2009. Subjects were children who suffered from dengue virus infection due to clinical diagnosis based on WHO criteria. Data was taken from medical record. Variables analyzed consisted of age, sex, clinical manifestations including hepatomegaly, jaundice, hepatic encephalopathy, and circulatory failure; laboratory findings including serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT). The data was analyzed using chi-square and t-test with 95% confidence interval. We found that from 72 patients, 34 patients had hepatomegaly, 4 patients had hepatic encephalopathy, and 52 patients with elevated serum transaminases level. There were significant differences in elevated AST level (mean difference 28.5 [9.4 to 47.5], p 0.004) and hepatomegaly (proportion difference 0.3 [0.1 to 0.5], p 0.018) related to the severity. Elevated ALT level >3 fold (PR 4.1, 1.4-11.9, p 0.008) and hepatomegaly (PR 3.5, 1.2-10.1, p 0.018) associated with circulatory failure. In conclusion, manifestations of liver involvement in children with dengue infection in this study were hepatomegaly, elevated serum transaminases level, and hepatic encephalopathy. Elevated ALT level >3 fold and hepatomegaly associated with circulatory failure.

Keywords: children, dengue infection, liver involvement.

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INTRODUCTION

Recently dengue infection is still be endemic in developing country including Indonesia. The high mortality associated dengue infection is about 24000 cases per year worldwide. There are wide varieties in clinical findings from asymptomatic until severe cases. (Kumar & Tripathi 2008). Hepatic disorders commonly happen in dengue cases. It can because of direct sitopathologic effect of virus to hepatocyte, or impact of

immunologic reaction in dengue infection. Hepatic disorders associated dengue infections are commonly reported among adult cases, unusual in children. (Kumar & Tripathi 2008, Fadilah et al. 2000) This research will analysis hepatic disorders associated dengue infection among pediatric patients. This retrospective study will be done in Soetomo General Hospital, March 2008 until April 2009.

MATERIALS AND METHODS

This is a case-control study which data were collected from medical record by data collecting form. Variables analysed were age, sex, hepatomegaly, shock, jaundice, hepatic encephalopathy, and transaminase level. The inclusion criteria were all patients with dengue infection admitted in Soetomo General Hospital March 2008 until April 2009. The diagnosis was based on WHO criteria 1997. Subjects were grouped into five groups, including dengue fever, dengue hemorrhagic fever grade 1, dengue hemorrhagic fever grade 2, dengue hemorrhagic fever grade 3, and dengue shock syndrome. Dengue infection without circulatory dysfunction including dengue fever, dengue hemorrhagic fever grade 1, and grade 2. Dengue infection with circulatory dysfunction including dengue hemorrhagic fever grade 3 and dengue shock syndrome. Serum transaminase level was checked in every patients, including aspartate aminotransferase and alanine aminotransferase. The groups are normal, 1 – 3 fold elevation, and > 3 fold elevation. Statistics analysis uses X² and t test with 95% confidence interval. Significant if $p < 0.05$.

RESULTS

Of 72 patients, 31 (43.1%) was male and 41 (56.9%) with sex ratio 1 : 1.32. Mean age was 4.93 years of old (range 1-15 years) and the greater was >4 years of age.

Table 1. Characteristics of 72 subjects based on age and sex

| Variables | Number of patients (%) |
|-----------------------------------|------------------------|
| Age (years) mean \pm SD (range) | 4,93 \pm 2,91 (1-15) |
| 0-<1 | 3 (4.2) |
| 1-<4 | 14 (19.4) |
| ≥ 4 | 55 (76.4) |
| Sex | |
| Male | 31 (43.1) |
| Female | 41 (56.9) |
| Sex ratio (male : female) | 1 : 1.32 |

Table 2 revealed 22 (30.6%) patients with shock, 4 (5.6%) patients with hepatic encephalopathy, 34 (47.2%) patients with hepatomegaly, and no patients with jaundice. Serum transaminase level was normal in 20 (27.7%) patients and increased in ALT or AST in 52 (72.3%) patients. Median ALT was 89 IU and AST was 92.5 IU. Mean ALT was 93.75 ± 63.55 IU and mean AST was 147.17 ± 187.57 IU.

Table 2. Manifestations of liver involvements among subjects

| Variables | Number of patients (%) |
|--|------------------------|
| Hepatomegaly | 34 (47.2) |
| Jaundice | 0 (0) |
| Hepatic encephalopathy | 4 (5.6) |
| Aspartate aminotransferase level, mean | 93.75 ± 63.55 |
| Normal (<36 IU) | 16 (22.2) |
| 1-3 fold elevation (36-108 IU) | 31 (43.1) |
| 0-<1 years | 0 |
| 1-<4 years | 7 |
| ≥ 4 years | 24 |
| >3 fold elevation (>108 IU) | 25 (34.2) |
| 0-<1 years | 0 |
| 1-<4 years | 4 |
| ≥ 4 years | 21 |
| Alanine aminotransferase level, mean | 147.17 ± 187.57 |
| Normal (<45 IU) | 4 (5.6) |
| 1-3 fold elevation (45-135 IU) | 47 (65.3) |
| 0-<1 years | 2 |
| 1-<4 years | 11 |
| ≥ 4 years | 34 |
| >3 fold elevation (>135 IU) | 26 (36.1) |
| 0-<1 years | 0 |
| 1-<4 years | 3 |
| ≥ 4 years | 18 |

The number of patients in ALT group, 1-3 fold elevation was higher than >3 fold elevation, group of >4 years was the greatest. The results were similar in AST group.

Table 3 compared clinical manifestations and serum transaminases level from patients with hepatic disorders with severity of dengue infection. The X² test showed significant comparison in hepatomegaly (p 0.018), hepatic encephalopathy (p 0.042), and increasing ALT level (p 0.039) with severity of dengue infection. There were no significant comparison between increasing AST and type of infection with severity of dengue infection. Table 4 described association between manifestations of hepatic disorders and circulatory dysfunction. There was significant association between >3 fold elevation ALT (PR 4.1; 1.4 – 11.9; p 0.008) and hepatomegaly (PR 3.5; 1.2 – 10.1; p 0.018) with circulatory failure. In this study, there were 4 patients with hepatic encephalopathy. They all had increasing AST and ALT > 3 fold elevation and hepatomegaly, 2 with dengue hemorrhagic fever grade 4, 2 with dengue hemorrhagic fever grade 1, 2 with primary infection, and 2 with secondary infection.

Table 3. Comparing variables between dengue fever and dengue hemorrhagic fever

| Variable | DF n=18 | DHF I n=24 | DHF II n=8 | DHF III n=15 | DHF IV n=7 | p value |
|----------------------------------|------------|---------------|---------------|-----------------|---------------|---------|
| Hepatomegaly | 3 | 13 | 3 | 11 | 4 | 0.018* |
| Hepatic encephalopathy | 0 | 2 | 0 | 0 | 2 | 0.042* |
| Aspartate aminotransferase level | | | | | | |
| Normal (<36 IU) | 8 | 3 | 0 | 3 | 2 | 0.039* |
| 1-3 fold elevation (36-108 IU) | 9 | 12 | 3 | 4 | 3 | |
| >3 fold elevation (>108 IU) | 1 | 9 | 5 | 8 | 2 | |
| Alanine aminotransferase level | | | | | | |
| Normal (<45 IU) | 3 | 0 | 0 | 0 | 1 | NS |
| 1-3 fold elevation (45-135 IU) | 12 | 18 | 4 | 10 | 3 | |
| >3 fold elevation (>135 IU) | 3 | 6 | 4 | 5 | 3 | |
| Type of infection | | | | | | |
| Primary | 7 | 7 | 1 | 2 | 0 | NS |
| Secondary | 11 | 17 | 7 | 13 | 7 | |

*p<0.05 (significant)

Table 4. Association between manifestations of liver involvement and circulatory failure among dengue infection children in this study

| Variable | With circulatory failure (n) | Without circulatory failure (n) | PR (95% CI) | p value |
|------------------------|------------------------------------|---------------------------------------|------------------|---------|
| Elevated AST level | | | | |
| 1-3 fold elevation | 13 | 34 | 0.5 (0.2 – 1.5) | 0.218 |
| >3 fold elevation | 8 | 13 | 1.9 (0.7 – 5.5) | 0.345 |
| Elevated ALT level | | | | |
| 1-3 fold elevation | 7 | 24 | 0.7 (0.2 – 1.9) | 0.450 |
| >3 fold elevation | 10 | 15 | 4.1 (1.4 – 11.9) | 0.008* |
| Hepatomegaly | 15 | 19 | 3.5 (1.2 – 10.1) | 0.018* |
| Hepatic encephalopathy | 2 | 2 | 2.4 (0.3 – 18.2) | 0.385 |

PR, prevalence ratio; CI, confidence interval

*p<0.05 (significant)

Table 5. Hepatic encephalopathy

| Cases | Aspartate aminotransferase level (IU) | Alanine aminotransferase level (IU) | Shock | Hepatomegaly | Severity of dengue infection | Type of infection |
|-------|---|---|-------|--------------|------------------------------------|----------------------|
| 1. | 220 | 345 | + | + | DHF IV | Secondary |
| 2. | 241 | 293 | - | + | DHF I | Primary |
| 3. | 254 | 214 | + | + | DHF IV | Secondary |
| 4. | 544 | 1014 | - | + | DHF I | Primary |

DISCUSSION

Recently dengue infection is still be the major health problem in developing countries including Indonesia. The mortality associated dengue infection is still high rate. The recent studies showed that liver involvement had serious contribution in morbidity and mortality dengue infection. The other study also said about liver as a major target organ of dengue virus (Fadilah et al. 2000).

Liver involvement is one of atypical manifestations of dengue infection. Gulati (2007) showed atypical manifestations of dengue infection including central nervous system, gastrointestinal tract, liver, kidney, cardiovascular tract, musculoskeletal, and lymphoreticular system. Atypical manifestations of liver organ include fulminant liver failure, cholecistitis, and pancreatitis. The liver dysfunction have wide variations, include increasing AST or ALT, alkaline phosphatase,

bilirubin, and encephalopathy, liver failure, coma, until multi organ dysfunction (Itha & Kashya 2005).

We had liver manifestations of dengue infections in this study include increasing serum transaminases level, hepatomegaly, and hepatic encephalopathy. Other researchs by Dhooria (2008) showed liver dysfunction in dengue infections included increasing serum transaminases level more than 3 fold elevation. Wiwanitkit (2007) revealed increasing serum AST or ALT more than 200 IU and hepatic encephalopathy as liver involvement in dengue infection.

We had 42 (77%) dengue patient with increasing serum AST or ALT > 3 fold elevation. That is higher than Dhooria's study (2008) in India which performed 14.8% dengue patient had increasing serum transaminase level > 3 fold elevation. Similar with Wiwanitkit's study (2007) in Thailand performed 34.6% dengue patient had increasing AST or ALT > 200 IU. In this study, we had 4% patient with hepatic encephalopathy. It is higher than Dhooria's study had 0.5% cases and Wiwanitkit's study had 2.6% cases. We had 47% with hepatomegaly and no jaundice. Dhooria showed hepatomegaly in 87% cases and also no jaundice. This study showed significant association between circulatory failure with increasing ALT > 3 fold elevation. Different with Wiwanitkit performed no significant association between increasing transaminase level with circulatory failure. We also performed significant association between hepatomegaly and circulatory failure. Instead of inflammation process and virus effect, shock cause circulatory failure lead to hypoxic hepatic dysfunction (Seneviratne & Malavige 2006).

CONCLUSION

Manifestations of liver involvement in children with dengue infection in this study were hepatomegaly, elevated serum transaminases level, and hepatic encephalopathy. Elevated ALT level >3 fold and hepatomegaly associated with circulatory failure.

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