Clinical manifestations of early childhood dengue virus infection in Thailand

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ABSTRACT

Introduction: Clinical manifestations of dengue infection has a wide spectrum. This study aimed to describe and compare the clinical aspects of dengue infection in early childhood and those in older children.

Materials and Methods: All dengue patients hospitalised at King Chulalongkorn Memorial Hospital, Bangkok, Thailand during 1987-2008 and aged 0-15 years were included. All parameters were compared between patients in two groups: aged 0-2 years and >2-15 years.

Results: Of the 2,221 children who were diagnosed with dengue, 179 were children aged 0-2 years compared with 2,042 children aged >2-15 years. The early childhood group presented significantly more frequently with hepatomegaly, drowsiness, diarrhoea, rash, convulsions, splenomegaly, and unusual manifestations. Dengue fever (DF) was more common in the early childhood group and dengue haemorrhagic fever (DHF) was less common. The mortality rate of the early childhood group was 1.67%, which was significantly higher than that of the comparative group. Approximately 65% of study subjects were serologically proven to have primary infection, compared to 9.8% of older children.

Conclusions: Clinical manifestations of dengue infection in early childhood are different in some aspects from those of dengue infection in older children, and mortality is higher. To effectively prevent dengue infection morbidity and mortality in children, it is essential that clinicians correctly recognize and diagnose dengue infection, particularly in early childhood.

KEYWORDS:
Dengue infection, Early childhood, Morbidity, Mortality, Thailand

INTRODUCTION

Dengue infection is a major health problem of Southeast Asia and the West Pacific.[1] Estimates of the disease burden suggest that there are nearly 100 million symptomatic dengue infections worldwide every year with the majority (75%) occurring in Asia and the West Pacific.[2] Disease incidence and deaths remains highest in children ≤15 years and case fatality rates were highest in young children.[3] The clinical manifestations of dengue virus infections have a wide spectrum, ranging from mild acute febrile illness to classical dengue fever (DF), dengue haemorrhagic fever (DHF), and dengue shock syndrome (DSS).[4]

In Thailand, rate of dengue infection in children is significantly increasing each year.[5] Additionally, a growing number of dengue infections are related to unusual manifestations in children with dengue, such as severe involvement of the liver, brain, kidney, or heart.[6-10] It has been shown that clinical manifestations of dengue infections during early childhood differ from those that occur in older children; furthermore, the case-fatality among infants with severe dengue disease is higher than that in older children.[5] Because of the bigger sample size, it should have a power in determining the mentioned difference. And there is no specific treatment for dengue infection, and the outcomes depend on early recognition of infection and careful monitoring of the patients. Therefore, we conducted this study to describe the clinical aspects and complications of dengue infection in early childhood and compare them with those in older children.

MATERIALS AND METHODS

This retrospective study was conducted in the Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand from 1987 to 2008. Inclusion criteria included 1) children aged 0-15 years who were admitted to King Chulalongkorn Memorial Hospital, 2) clinical diagnosis and disease severity of dengue virus infection, using the 1997 World Health Organization (WHO) criteria[11], and/or 3) confirmed dengue serological diagnosis, using hemagglutination inhibition test and/or an enzyme-linked immunosorbent assay (ELISA).

Patients were classified into two groups: children aged 0-2 years (early childhood group) and children aged >2-15 years (comparative group). Primary and secondary dengue virus infections were classified according to the serological criteria.[12] Data collected from medical records included symptoms and signs and laboratory findings of the patients. All parameters were compared between groups.

This study obtained ethics approval from the Forum for Ethical Review Committees of Srinakharinwirot University. Descriptive data were analyzed using SPSS 18.0. Variables were compared by chi-square test. A $p < 0.05$ was considered to be statistically significant.

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Table I: Symptoms and signs of the early childhood group (aged 0-2 years) in comparison to older children (aged >2-15 years) with dengue virus infections

Symptoms	0-2 years (n=179)	>2-15 years (n=2,042)	p-value
Days of fever prior to admission	4.4	4.9	NS
Hepatomegaly (%)	82.1	74.3	0.02
Coryza (%)	5.0	3.4	NS
Vomiting (%)	50.8	69.0	<0.0001
Drowsiness (%)	62.0	30.9	<0.0001
Diarrhoea (%)	31.2	18.0	<0.0001
Rash (%)	73.1	40.0	<0.0001
Convulsions (%)	17.8	1.3	<0.0001
Positive tourniquet test (%)	17.7	33.1	<0.0001
Splenomegaly (%)	3.3	0.7	<0.0001
Abdominal pain (%)	10.0	44.1	< 0.0001
Bleeding (%)	23.3	30.9	0.034
Unusual manifestations (%)	3.9	1.0	0.001

Table II: Laboratory findings of the early childhood group (aged 0-2 years) in comparison to older children (aged >2-15 years) with dengue virus infections

	0-2 years (n=179)	>2-15 years (n=2,042)	p-value
Hct max (vol%)	40.93	44.18	NS
Hct min (vol%)	33.19	37.18	NS
WBC min (cells/mm^3)	8,627.36	5,037.09	<0.0001
Platelet min (cells/mm^3)	62,473.57	76,167.42	<0.0001
Lymph max (%)	55.42	36.54	0.04
AL max (%)	10.29	10.71	NS
PMN max (%)	30.94	49.39	0.0039

Hct = hematocrit, max = maximum, min = minimum, mm^3 = cubic millimetre, Lymph = lymphocyte, AL = atypical lymphocyte, PMN = polymorphonuclear cell

Table III: Severity of dengue disease and serological response to dengue infections in all patients

Severity of dengue disease	0-2 years (n=179)	>2-15 years (n=2,042)	p-value
DF (%)	26.25	16.89	0.001
DHF (%)	73.74	82.85	0.002
DSS (%)	27.93	34.52	NS
Mortality rate	1.67	0.14	<0.0001
Serological response	**(n = 165)**	**(n = 1,872)**	
Primary infection (%)	107 (64.85)	185 (9.88)	<0.0001
Secondary infection (%)	58 (35.14)	1,687 (90.12)	<0.0001

Table IV: Severity of dengue disease classified by serological response

Primary infection	0-2 years (n=165)	>2-15 years (n=1,872)	p-value
DF (%)	30.84	44.32	<0.0001
DHF (%)	69.16	55.68	0.029
DSS (%)	26.17	5.41	0.004
Secondary infection			
DF (%)	22.41	14.38	<0.0001
DHF (%)	77.59	85.62	<0.0001
DSS (%)	31.03	36.51	<0.0001

RESULTS

Of the 2,221 children aged 0–15 years and diagnosed with dengue, 179 were aged 0–2 years. Of these, 88 and 91 were males and females respectively. Prior to admission, nearly all patients had a fever for an average of 4.4 days. Compared with 2,042 children aged >2-15 years, the early childhood group presented significantly more frequently with hepatomegaly, drowsiness, diarrhoea, rash, convulsions, splenomegaly and unusual manifestations (Table I).

In the early childhood group, the mean maximal haematocrit value (Hct max) was 40.93 volume%; the mean minimal value of the white blood cell (WBC min) count was 8,627 cells/mm^3; the mean of maximal percentage of lymphocytes, atypical lymphocytes, and polymorphonuclear cells was 55.42%, 10.29% and 30.94%, respectively, and the mean minimal value of the platelet count was 62,473 cells/mm^3 (Table II).

DF was more common in the study group and DHF was less common, but there was no significant difference in rates of DSS between groups. The mortality rates of the early childhood group was 1.67%, which was significantly higher than that of the comparative group. Approximately 65% of children aged 0-2 years were serologically proven to have primary dengue infection, while only 9.8% of older children had primary dengue infection (Table III).

DHF comprised approximately 70% of cases with primary infection among children aged 0-2 years. Moreover, DSS comprised approximately 26% of cases in the early childhood group who were serologically proven to have primary infection (Table IV).

DISCUSSION

Dengue virus is the causative agent of a wide spectrum of clinical manifestations and is transmitted to humans by *Aedes aegypti* and *Aedes albopictus* mosquito species. This mosquito-borne arboviral infection is endemic in Asia, the Eastern Mediterranean, the Americas, and Africa. The common manifestations of dengue infection is fever, vomiting, macular rash, myalgia, hepatomegaly, haemorrhagic manifestations including a positive tourniquet test, petechiae, purpura, ecchymosis, epistaxis, gum bleeding, and hematemesis and/or melena with no apparent symptoms or signs of respiratory tract infection.[4,13] Our study showed the early childhood group presented significantly more frequently with hepatomegaly, drowsiness, diarrhoea, rash, convulsions, splenomegaly and unusual clinical manifestations than comparative group. Patients with unusual manifestations tended to be younger and to have higher mortality rate than older children. The other common manifestation of dengue infection in early childhood is hepatomegaly but splenomegaly is uncommon. As previous studies have reported splenomegaly as an atypical presentation of dengue infection; the frequency of splenomegaly among childhood cases of dengue infection varies between studies.[14-18] In this study, we found that splenomegaly was more common in the early childhood group than in older children. In addition, 18% of the early childhood group in this study developed convulsions, which also are more common due to high grade of fever.

Children aged 0-2 years of age tend to have higher WBC counts and a higher percentage of lymphocytes and polymorphonuclear cells.[19] In contrast, our study showed that patients in the early childhood group had the mean minimal value of the WBC count and the mean of maximal percentage of lymphocytes more than those in the older age group. However, the mean maximal percentage of polymorphonuclear cells in patients aged 0-2 was lower than that in the older age group. The mean minimal value of the platelet count in the early childhood group was significantly lower than of the comparative group; however, we found that clinical of bleeding was significantly less common in the early childhood group than in the older age group in this study. Clinical of bleeding in dengue infection may be caused by thrombocytopenia, vasculopathy, platelet dysfunction, or coagulopathy.[20]

In addition, we have only one case of congenital dengue patient (vertical transmission) in the early childhood group.[21] Coinfections in dengue patients have been seen in our study, these may lead to missed diagnosis and treatment of dengue infection.[22]

Explanatory hypotheses for the mechanism of DHF/DSS have remained a topic of debate for decades.[4] Two distinct hypotheses to explain this mechanism have been debated between secondary infection or antibody enhancement and viral virulence. Antibody enhancement hypothesis was first described in 1977.[23] According to this hypothesis, a pre-existing antibody to dengue virus plays an important role in the development of severe disease symptoms; additionally, patients with secondary infection tend to be significantly more likely to develop shock compared to those with primary infection.[24] Although secondary dengue infection remains the strongest known hypothesis for explaining the mechanism of DHF/DSS, our study shows that various severities of dengue diseases, as well as both primary and secondary dengue infection, can occur in all age groups among children. This confirmed the observation that DSS can occur with primary infection in all age groups.

Dengue infection can only be prevented through controlling the mosquito vectors and administering the dengue vaccine.[25] The first dengue vaccine (CYD-TDV; Dengvaxia®, Sanofi Pasteur, Lyon, France) was licensed for use in individuals aged 9-45 years old in Thailand on October 2016, where dengue is endemic.[25,26] This vaccine has shown good efficacy in older children; however, in this study the mortality rate of children aged 0-2 years old who were infected with dengue was 1.67%, which was a significantly higher rate than that of older children. This finding is similar to mortality rates reported in a previous study.[5] As the licensed dengue vaccine is not indicated for use in this age group, development of new dengue vaccines with a good efficacy and favourable safety for use in younger children are necessary.

DISCUSSION AND CONCLUSIONS

Dengue virus infection during early childhood is not uncommon. The majority of children aged 0-2 years in this study acquired primary dengue infection. Clinical manifestations and complications of dengue infection vary between age groups. To effectively prevent dengue infection

morbidity and mortality in children, it is essential that clinicians correctly recognize and diagnose dengue infection, particularly in early childhood. Further studies to increase the understanding of dengue pathogenesis and disease severity in a well-defined cohort population between age groups is warranted.

CONFLICT OF INTEREST

None to declare.

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