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PROFILE OF PEDIATRIC PATIENTS WITH DENGUE FEVER/DENGUE HEMORRHAGIC FEVER OVER A FIVE-YEAR PERIOD (2000-2004)

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KEYWORDS
dengue, dengue fever, dengue hemorrhagic fever

ABSTRACT

Objectives: This study was conducted to determine the clinico-demographic profile of pediatric patients who were admitted for dengue infection at the Research Institute for Tropical Medicine (RITM) from 2000 to 2004.

Methods: This is a retrospective, descriptive study. Charts of patients who were less than 19 years of age and were admitted at the RITM due to confirmed dengue (using paired dengue HI titer results) were reviewed.

Results: Two hundred patients qualified for the study. The mean age of the patients was ten years ± four years SD with an equal sex distribution. The most common chief complaint was fever while petechiae were the most common evidence of bleeding. The mean hematocrit among patients was 42 ± 5 vol % and platelet count of 129 ± 53/mm^3. Fifty-one percent of the patients had Dengue Hemorrhagic Fever grade II. All subjects were discharged with improved condition. Among the patients, 49% had acute secondary dengue infection, 32% had recent secondary dengue infection, and only 13% had acute primary dengue infection.

Conclusion: The clinico-demographic profile of patients involved in the study was very similar to that of other studies done, both locally and abroad. By using Spearman's correlation of ranks, the study showed that there was no significant relationship between the severity of dengue infection based on the World Health Organization (WHO) Grade and whether it was a primary or secondary infection with r=.018, p-value=.025.

Dengue is a major health problem in most tropical and subtropical areas.[1] It is the most common arboviral infection and can cause high morbidity and mortality rates.[2] Its incidence has increased dramatically in recent decades with over a million cases reported from the Western Pacific Region within a ten-year period, from 1990-1999, including the Philippines, which accounted for 105,000 cases with a mortality rate of 1.6%.[3] So far, 2,330 dengue cases had been reported in the Philippines for the first half of 2004—with 16 deaths (0.7%); [4] thus, it has remained to be a major health concern for decades.

Dengue is due to infection with the dengue virus (belonging to Family Flaviviridae), which has four distinct viral serotypes (1 to 4), and is transmitted by the bite of infected mosquitoes (*Aedes sp.*).[3-5] Infection may result to: 1) dengue fever (DF), which is an acute febrile illness with headache, retro-orbital pain, myalgia, arthralgia, rash, nausea and vomiting; and 2) dengue hemorrhagic fever (DHF), which is characterized by fever, thrombocytopenia, hepatomegaly, increased capillary fragility and permeability, and bleeding tendencies, according to the WHO case definitions.[6]

Definitive diagnosis is made by viral isolation or by detection of viral antigen in body fluids. Other serological tests may also be done to confirm infection.[5,10-14] However, at the Research Institute for Tropical Medicine (RITM), the dengue hemagglutination-inhibition test (HI test) was the only diagnostic examination available to confirm dengue infection during the conduct of this research. The HI test is a simple, sensitive and reproducible test which is based on the ability of the viral antibodies to inhibit agglutination. It has the following advantages: use of reagents that may be locally prepared; and allows the clinician to determine whether the infection is primary or secondary.[6,11-12] However, its disadvantages include: the requirement for a paired convalescent sera for interpretation; and it does not distinguish infection due to other closely-related flaviviruses, such as the Japanese encephalitis virus. This was pointed out the study by Yamada, et. al.[11] in 2003 which showed cross-reactivity of Dengue HI assay with Japanese encephalitis B virus.

OBJECTIVES

The main objective of this research is to determine the clinical profile of pediatric patients with dengue infection within a five-year period (2000 to 2004) at the RITM.

Other data collected and analyzed included whether the infections are primary or secondary, based on the dengue HI assays; and whether the grading of the severity of dengue infection correlates with the dengue HI assays of the patients (primary or secondary infection).

SIGNIFICANCE OF THE STUDY

By reviewing the clinico-demographic profiles of pediatric patients with dengue infection, the study provided a source of epidemiological data on dengue infection in the Philippines. It also re-evaluated the correlation of the diagnosis of infection (primary or secondary) to the grading of the severity of illness. Furthermore, by obtaining data from an infectious disease referral center equipped with a reference laboratory, the results of the study may be used as a baseline for further studies on dengue infection.

ETHICAL CONSIDERATIONS

The study protocol was approved by the institutional ethics committee of the Research Institute of Tropical Medicine and the National Institute of Health.

MATERIALS AND METHODS

Study Design: The study utilized a descriptive-retrospective design.

Study Population: The subjects for this study were patients less than 19 years old and who were admitted at the RITM, regardless of discharge diagnosis, and with Dengue HI paired sera titers within a five-year period, from 2000 to 2004. Patients without paired sera samples

for dengue HI test and those who were more than 19 years old were not included in the study. Patients whose charts could not be retrieved from the medical records section of the institution were likewise excluded from the study.

Data Collection: A list of patients with paired dengue HI sera results from 2000 to 2004 was obtained from the Virology section of the RITM. Another list of patients who were diagnosed with DF, DHF, or dengue shock syndrome (DSS) was also obtained from the institution's medical records section. The charts of patients who were less than 19 years of age and with dengue HI titers and those with other diagnoses, but with paired dengue HI titers were also retrieved and reviewed.

The criteria for determining whether an infection is primary or secondary through the HI test was established by the WHO.[6] The criteria for primary infection are: there should be a fourfold increase in the HI titer for a paired set of sera specimens; and the titer in the convalescence phase should be <1,280. For secondary infection, the criteria are: a fourfold increase in titer; and a value of ≥2,560 in the convalescence phase.

For statistical purposes, and in order to present the clinical profiles in numerical values, an arbitrary scoring index based on the WHO criteria was made to grade the severity of illness. For grade I, the patient had a minimum score of three out of four (fever, hemoconcentration and either petechiae/ (+) tourniquet test or rash, any other non-specific signs and symptoms). The presence of any spontaneous bleeding, in addition to the criteria for grade I, qualified a patient to have grade II severity of illness (total score of 5 to 6). The presence of either hypotension or weak pulses/cold extremities (score of 3 was assigned to each) was an additional criterion for a patient to be labeled as grade III, with a possible total score of eight-to-12. A patient with profound shock was given an additional score of four and was labeled as grade IV, with a possible total score of 13-to-17.

STATISTICAL ANALYSIS

All numerical data were summarized using mean and standard deviations, frequency distribution and percentages.

Pearson correlation was used to determine the association between two continuous numerical variables, such as the dengue severity scores and the corresponding HI titers; while, Spearman's rho correlation was utilized to determine the association of discrete categorized data with rank properties. All r-values and their corresponding p-values were calculated using the Statistical Package for the Social Sciences (SPSS Version 10.1). All statistics were set at a 0.05 level of significance.

Table 1. Arbitrary scoring index for the grading of the severity of infection.

Signs and symptoms	Grade I	Grade II	Grade III	Grade IV
Fever	+1			
Hemoconcentration	+1			
Rash/petechiae/ (+) tourniquet test	+1			
Abdominal pain/hepatomegaly/ cough/colds/ headache/weakness/ malaise/etc	+1			
Epistaxis/gum bleeding/GI bleed		+2		
Weak pulses/cold extremities			+3	
Hypotension			+3	
Profound shock				+5
POSSIBLE SCORE	3-4	5-6	8-12	13-17

RESULTS

There were 566 patients who were diagnosed with dengue infection and were admitted at RITM from 2000 to 2004, while there were 268 patients who had dengue HI titers done on them. Of these patients, 27 were

more than 19 years of age, 22 were out-patient department (OPD) patients, while the charts of 19 patients could not be found. Thus, only 200 patients qualified for the study.

The youngest patient was four months old, while the oldest was 18 years old—with a mean of ten years old plus four years SD (Table 2). Majority of the patients were between six-to-12 years of age (as shown in Figure 1), which accounted for 64% of the patients involved in the study. An equal sex distribution was noted. Most of the patients came from the area of Muntinlupa/Las Piñas (62%); while 16% hailed from Laguna; 10% from Cavite; and only 8% from other areas in Metro Manila.

Clinical Profile

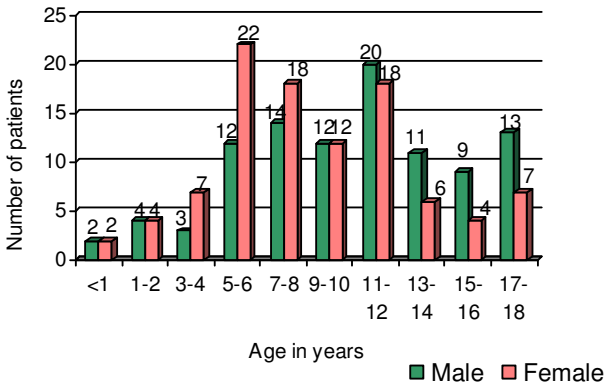
Illness among the patients involved in this study was heralded by fever. The earliest time for admission from the onset of clinical symptoms was one day, while the longest was ten days (mean of 4 ± 1). The average hospital stay was five days (± 4 days SD), as shown in Table 2.

The earliest documented duration of fever was two days, while the longest was at 23 days. While admitted in the hospital, the longest persisting febrile episode was 13 days.

Table 2. Demographic profile of patients confirmed to have Dengue infection by HI.

Characteristic	Frequency, (%) N=200
Age	
Range	4 months to 18
(Mean ± SD) years	10 ± 4
Sex	
Male	100 (50)
Female	100 (50)
Address	
Muntinlupa/Las Pinas	123 (62)
Laguna	32 (16)
Cavite	20 (10)
Metro Manila	16 (8)
Batangas	2 (1)
Others	7 (4)

Figure 1. Age and sex distribution of patients confirmed to have Dengue infection by HI.



Fever was the most common chief complaint (72%); followed by epistaxis (10%), abdominal pain and weakness (4% each), rashes (3%), and gum bleeding, loss of appetite and hematemesis (2% each) (Table 4).

Pertinent physical exam findings included fever for all patients, hepatomegaly in 43%, petechiae in 29%, epistaxis in 17%, gum bleeding in 15%, rash in 13%, hypotension in 12%, and cold extremities in 7%. Of the patients with petechiae, 15 of them had recorded positive in the tourniquet test. However, it was not indicated if tourniquet test was performed on the other patients.

The most common evidence of bleeding, which may or may not be present on admission, was petechiae (42%); followed by epistaxis (31%), hematemesis (15%), and then gum bleeding (12%). Four patients (2%) had episodes of melena.

Hematocrit ranged from 29 to 64 volume %, with a mean of 42 ± 5 vol %, while platelet count averaged 129,000 + 53,000 /mm3 (range of 38,000 to 418,000/mm3). There were 63 patients who had platelet count of less than 100,000 during admission. All subjects were discharged in improved conditions.

Serological Profile

The serological (HI titers) profiles of the patients were reviewed. From said patients, 49% had acute secondary dengue infection, 32% had recent secondary dengue infection,

while only 13% had acute primary dengue infection as depicted in Table 5. Identification of the infection as either acute primary or secondary dengue was noted in 2% of cases, while 3% of cases were identified as not dengue. One patient had an indeterminate serologic picture. Of the 200 charts reviewed, there were five patients who reported a previous history of dengue infection: one was serologically confirmed as primary flavivirus infection; two as acute flavivirus infection; and the other two as recent secondary flavivirus infection.

Table 3. Fever profile of patients.

Characteristic	Frequency (%) N=200
Time interval from onset of Illness to hospital admission	
Range (days)	1 to 10
(Mean ± SD) days	4 ± 1
Length of Hospital stay	
Range (days)	2 to 47
(Mean ± SD) days	5 ± 4
Duration of fever	
Range (days)	2 to 23
(Mean ± SD) days	5 ± 2
Number of days of fever in the hospital	
Range (days)	0 to 13
(Mean ± SD) years	1 ± 1

Correlation between severity of dengue fever and HI titer

Table 6 stratified the dengue severity (using the arbitrary scoring index shown in Table 1) based on HI titers. Acute and recent secondary infections were grouped together, while non-dengue and non-interpretable titers were labeled as unclassified.

By interpreting the table vertically, majority (67%) of the primary dengue infections were grade II in severity, 17% were grade I, and 12% were grade III; these accounted for 12% of the total number of patients involved in the study. Most secondary infections (52%) were grade II, while 24% were grade 1, 20% were grade 3 and 2% were grade 4, which made up 83% of the total number of patients in the study. Seventy-five percent of acute primary or secondary infections were grade I and 25% were grade IV. Of the patients belonging to "unclassified" category, three (50%) were grade II and two (31%) were grade III. Using grading of severity of illness as the take off point, out of the 200 patients, 53% were grade II, 24% were grade I, 20% were grade III, 1.5% were grade IV, and 3% had other diagnoses.

Dengue Severity and Past Infection

Among those without past histories of dengue infection, 103 patients were grade II, 46 patients were grade I, 39 patients were grade III, and one patient was diagnosed as grade IV. For those with histories of dengue infection based on memory recall, one patient was diagnosed as grade III, two patients were grade II, and one patient was grade I; this is shown in Table 7.

Table 8 shows the corresponding HI titers of patients with history of dengue infection. Four of the five patients who claimed to have histories of dengue infection had secondary flavivirus infection based on dengue HI titers—one was discharged on the diagnosis of SVI rather than DHF. However, one who claimed to have a history of dengue infection turned out to have primary flavivirus infection.

Table 9 shows that there was no significant relationship between the severity of dengue infection based on the WHO Grade and the revelation of the HI titer as either primary infection or secondary infection (recent or acute) with r=.018, p-value=.025.

Table 4. Clinical profile of patients (N=200).

Characteristic	Frequency, (%)
Chief Complaint	
Fever	148 (72)
Epistaxis	21 (10)
Abdominal pain	8 (4)
Weakness	7 (4)
Rash/petechiae	5 (3)
Gum bleeding	4 (2)
Loss of appetite	3 (2)
Hematemesis	3 (2)
Vomiting	1 (1)
Other symptoms*	
Abdominal pain	96 (48)
Vomiting	59 (30)
Cough/coryza	48 (24)
Decreased appetite	48 (24)
Headache	36 (18)
Physical Exam Findings*	
Fever	200 (100)
Hepatomegaly	85 (43)
Petechiae	58 (29)
Epistaxis	33 (17)
Gum bleeding	30 (15)
Rash	25 (13)
Low blood pressure	23 (12)
Cold extremities	13 (7)
Signs of bleeding*	
Petechiae	**83 (42)**
Epistaxis	61 (31)
Hematemesis	30 (15)
Gum bleeding	24 (12)
Melena/hematochezia	4 (2)
History of previous dengue infection	5 (3)
Yes	195 (97)
No	
Hematocrit	
Range	29 to 64
(Mean ± SD) volume %	42 ± 5
Platelet count	
Range	38,000 to 418,000
(Mean + SD) per cubic mm	129,000 ± 53,000

** More than 1 associated symptom/s, physical exam findings or bleeding manifestations may be seen in a single patient.*

Table 5. Serological profile of patients

Characteristic	Frequency, (%) N=200
Interpretation of Titers	
Acute Secondary Infection	99 (49)
Recent Secondary Infection	64 (32)
Acute Primary Infection	26 (13)
Acute Primary or Secondary Infection	4 (2)
Not dengue	6 (3)
Uninterpretable	1 (1)

Table 6. Cross tabulation of Dengue Severity using an arbitrary scoring index and HI Titer (N=200).

Final Diagnosis	1° Infection (%)	2° Infection (%)	Acute 1° or 2° infection (%)	Unclas-sified (%)	Total (%)
DHF 1	4(2)	40 (20)	3 (1.5)	0	*47 (24)*
DHF 2	16 (8)	86 (43)	0	3 (1.5)	*105 (53)*
DHF 3	3 (1.5)	34 (17)	1 (0.5)	2 (1)	*40 (20)*
DHF 4	0	3(1.5)	0	0	*3 (1.5)*
Other Diagnoses	1 (0.5)	3(1.5)	0	1 (0.5)	*5 (3)*
Total	*24 (12)*	*166 (83)*	*4 (2)*	*6 (3)*	*200 (100)*

Table 7. WHO dengue severity classification versus history of previous dengue infection.

Dengue Grade	No History (N=195)	With History (N=5)
1	46	1
2	103	2
3	39	1
4	3	0
Other diagnoses	4	1
Total	*195*	*5*

Table 8. Dengue HI titers of patients with history of dengue infection.

Final Diagnosis	HI titer result
DHF 1	Acute, secondary
DHF 2	Acute, primary
DHF 2	Recent, secondary
DHF 3	Acute, secondary
SVI	Recent, secondary

Table 9. Correlation of WHO severity classification and HI titer result.

WHO Severity Grading for Dengue Fever	Primary Infection	Secondary Infection
DHF 1	r= .018* p-value=.80	r = .025* p-value=.15
DHF 2		
DHF 3		
DHF 4		

*Significant correlation if p-value <.05, computed using Spearman's Correlation of ranks, SPSS Version10
r= 0 to 0.25 little or no association
r= 0.25 to 0.5 fair relationship
r= 0.5 to 0.75 moderate relationship
r= >0.75 strong relationship

DISCUSSION

Most of the patients involved in the study were between 6-to-12 years old. Our data was similar to a study on dengue fever among hospitalized children in Bandung, Indonesia[20] most of the patients were between 7 to 10 years of age. Similar findings were noted in studies made by Imlan[21] and by Sriprom[5] in Thailand, in which most patients were between five-to-12 years of age. Said age group may be vulnerable to dengue infection because they are the ones who attend school and leave the house to play in the fields and backyards; thus, they are more exposed to the mosquito vector. There was an equal sex distribution noted among the patients.

As to locality, majority of patients came from the Southern parts of Manila. This may be explained by the location of the institution which makes it more accessible to residents of that area.

Fever was the most common chief complaint; it was followed by epistaxis, abdominal pain, and weakness. Similar findings were also cited by Imlan, et. al[21] and by Reyes, et. al.[9] Mean duration of febrile episode was 5 ± 2 days, with the longest duration being 23 days in a patient who developed necrotizing fasciitis. For other signs and symptoms, abdominal pain was most commonly present, followed by rash, and then vomiting.

Platelet counts of <100,000/mm^3 were seen in 63 patients (32%): 50% of them were grade II; but 12 of the patients with thrombocytopenia were grade I. No patient had platelet counts of <20,000/mm^3. Capeding, et. al.[18] also had similar findings, with 37% of their patients developing thrombocytopenia of <100,000/mm^3.

Many of the patients had mild bleeding manifestations, but shock was uncommon. This was also noted in studies done in Metro Manila[8, 18, 23] wherein all patients involved were discharged with improved condition. This was in contrast to other studies done in Thailand[22] in which more than 30% of their patients developed shock due to massive blood loss. This contrast may be attributed to the skewed population involved in the study, since one of the inclusion criteria was for a patient to have a convalescent titer; thus, only those who were well enough to be discharged or to follow-up after seven days for the convalescent titer were included in the study. Some of the patients with a stormier course, or who may have died or went home against advice were, therefore, excluded from the study.

Petechiae (42%), epistaxis (31%) and hematemesis (15%) were the most common bleeding manifestations seen in patients in this study. Tourniquet test was done on 24 patients;

15 of whom turned out positive. Since the rest of the patients had no record of the test done on them, it was not known whether or not the tourniquet test was done on them. A study done by Imlan, et. al[21] among pediatric patients in Zamboanga City showed that 61% of their subjects had positive tourniquet test results, followed by petechiae in 55%, then epistaxis in 17%. Similar findings were also noted by Reyes, et. al[9] in a study among pediatric patients in Metro Manila. However, in the study made by Liu, et. al.[1] among adult patients in Taiwan, epistaxis was not common; it was present in only 2% of the subjects. Whether this phenomenon was due to a difference in the age group of subjects, compared to local studies made on pediatric subjects, may deserve some more investigation.

An arbitrary scoring index was assigned to each patient for statistical purposes, since many of the patients had final diagnoses which did not match the WHO criteria. Hence, the scoring index approximated the signs and symptoms seen in each patient based on WHO criteria. Out of 200 patients, 53% were grade II, 24% were grade I, 20% were grade III, 1.5% were grade IV, and 3% had other diagnoses. Of these, 166 (83%) had secondary flavivirus infection based on serological titers, while 24 (12%) had primary flavivirus infection. This result showed the endemicity of dengue in the Philippines, which can also be noted in other previous local studies.[8, 18, 21, 23]

Of the five patients who reported previous histories of dengue infection, four turned out to be secondary infections, while one was a primary infection. Due to the scarcity of patients who reported a previous history of infection, this study could not come up with a correlation between dengue severity and history of infection. However, regardless of history of previous infection, this study was able to show that no significant relationship can be established between severity of illness and whether infection was primary or secondary.

CONCLUSIONS/RECOMMENDATIONS

The clinico-demographic profile of patients involved in this study was very similar to that of other studies done, both locally and abroad, with majority of patients falling between the ages of five-to-12 years. Fever was present in all patients and was the most common chief complaint—with abdominal pain and vomiting as the most common associated symptoms. Bleeding manifestation was most commonly seen as petechiae, followed by epistaxis then hematemesis. Mean hematocrit among patients was 42 ± 5 vol % and platelet count of 129 ± 53/mm^3. Up to 51% of the patients had DHF grade II, while three patients diagnosed as DHF grade IV had secondary infection based on serological titers. Only five patients reported a previous history of dengue infection by memory recall: four of whom were confirmed to be secondary infection based on dengue HI titer; and one was a primary infection. Overall, 166 (85%) of the patients had secondary flavivirus infection based on serological tests which indicates the endemicity of dengue in the area. By using Spearman's correlation of ranks, no significant correlation can be established between the severity of illness and HI titer result. Therefore, whether the infection is primary or secondary, it cannot be said to be statistically significant when correlated with the severity of illness based on WHO criteria.

RECOMMENDATIONS

Based on the results of the study, the following recommendations are encouraged:

1. Conduct a similar study involving the adult population;
2. Conduct multi-center studies with other diagnostic modalities;
3. Follow-up patients with documented previous infection (i.e., serological titer/culture result) and compare severity of illness in future dengue infections.

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