DENGUE SURVEILLANCE IN METRO MANILA

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Abstract. In a one-year surveillance of dengue infection in four hospitals in Metro Manila, Philippines, 143 patients were enroled. Sixty seven were diagnosed by virus isolation and serology. Majority of patients had secondary antibody response. Only 5 patients developed dengue shock syndrome. Only dengue types 1 and type 2 were isolated. Highest incidence occurred among older children and young adults. Thrombocytopenia and hemoconcentration were observed in 37% and 77% of patients, respectively. There was no fatality. Several problems were identified in the course of the study which need to be corrected in order to have good quality surveillance data in future undertakings.

INTRODUCTION

Dengue fever and dengue hemorrhagic fever (DHF) remain a major cause of morbidity and mortality in the Philippines. Over the past years, dengue infection has increasingly become a significant public health problem and the present incidence rates indicate its endemicity in the country.

The virology laboratory of the Research Institute for Tropical Medicine (RITM) is the national reference center for dengue infection. It has well established capabilities for virologic studies. A review of the records at the virology laboratory showed definite dengue infection in only 38% of cases referred for virological studies. This, however, is an underestimate of the epidemiology of the disease in the country and could be due to the absence of an active surveillance system to monitor clinical cases as well as inaccessibility to a virology laboratory for diagnostic confirmation. As a result, a dengue epidemic may be near peak transmission before it is recognized. Thus, accurate knowledge of the transmission of dengue viruses is important for establishing effective disease control strategies.

The aim of the study was to develop an active clinical and virological surveillance system in some areas in Metro Manila and consequently to be able to make recommendations that would improve capabilities for prevention and control measures. The other aims of the study were to identify patients with dengue fever by virus isolation and specific serologic response, to study the risk factors related to disease manifestations and outcome, and to correlate the infecting serotype with clinical manifestations.

PATIENTS AND METHODS

Patients were enroled from four hospitals in Metro Manila, three private hospitals and a tertiary government hospital, for a period of one year. Physicians and parents were informed of the study. Patients included in the study were those who presented with acute febrile illness with no obvious primary focus of infection, with or without hepatomegaly, bleeding manifestations and circulatory collapse. Clinical data were obtained daily and entered into a standardized clinical form.

Virological studies were done at RITM. They included virus isolation using sensitive mosquito cell lines and serodiagnosis by the hemagglutination-inhibition test (HI). The infecting viral serotype was identified by immunofluorescence method using dengue type specific monoclonal antibodies.

Patients were monitored daily by a resident physician and were followed up to ten days or until discharge, whichever was longer. Blood specimens were drawn on admission for virus isolation and serology. Hematocrit and platelet counts were done until values became normal. A convalescent serum sample was collected at least seven days after the acute serum sample or until discharge, whichever was longer.

RESULTS

One hundred forty-three patients were enroled during the study period, from July 1992 to August 1993. Sixty-seven (47%) of dengue infections were diagnosed by virus isolation and or serology. Of these, 47 (70%) were confirmed by serology alone, 17 (25%) by virus isolation and 3 (5%) were diagnosed both by serology and virus isolation. Sixteen (11%) suspected cases of dengue were not proven to be dengue infections. Sixty cases (41%) were unconfirmed dengue infections because blood samples were unsuitable for virus isolation or uninterpretable by serology.

Of the 50 patients who were diagnosed serologically based on the antibody response using the World Health Organization criteria (WHO, 1995), primary antibody response was detected in 19 (38%) of the cases and definite secondary infection in 27 (54%). Either primary or secondary antibody response was observed in one patient and 3 patients had presumptive secondary infection. Only two dengue virus serotypes were isolated, type 1 and type 2. Type 1 was the dominant serotype in 16 (80%) of cases (Table 1).

Table 1

Laboratory diagnosis of confirmed dengue patients.

	No. of cases	%
I. Antibody response	50	
1°	19	38
2°	27	54
1°/2°	1	2
Probably 2°	3	6
II. Virus isolation	20	
Dengue type 1	16	80
Dengue type 2	4	20

The distribution of patients based on the WHO clinical classification against antibody response is shown in Table 2. Of the patients serologically and virologically proven for dengue infection, none had an illness more severe than DHF Grade III. There were no differences noted in the antibody responses of patients with dengue fever. A majority (82%) of patients with DHF Grade II had secondary antibody response whereas, there was no significant difference in the antibody response (primary or secondary) in patients who had DHF Grade III. No specific serotype was associated with dengue shock syndrome (DSS). There was no mortality.

Of the 67 laboratory-diagnosed dengue patients, 37 (55%) were boys and 30 (45%) were girls. Majority of patients (38%) belonged to 10-19 years age group, 23% were 1 to 4 and 5 to 9 years old, respectively, 13% were 12 years and above and only 3% were younger than one year old.

Non-specific signs and symptoms and hemorrhagic manifestations observed in the patients are shown in Table 3. The five most frequent manifestations were abdominal pain, headache, flushing, vomiting and nausea. Thrombocytopenia and hemoconcentration, which are laboratory features

Table 2

Serologic responses of confirmed dengue patients.

WHO clinical classification	* Antibody response (no. of patients)			Probably 2°	Total
	1°	2°	1°/2°		
DF	8	6	1	3	18
DHF					
Grade I	4	2	0		6
Grade II	4	9	0		11
Grade III	2	3	0		5
Grade IV	0	0	0		

* WHO antibody response classification

Table 3

Clinical manifestations and laboratory features of confirmed dengue patients.

Signs/symptoms	No. (%)	Laboratory features	No.(%)
Abdominal pain	35 (58)	Hemoconcentration	46 (77)
Headache	32 (53)	Thrombocytopenia	22 (37)
Flushing	32 (53)	Leukopenia	45 (75)
Vomiting	29 (48)		
Nausea	25 (42)	Tourniquet test (+)	52 (87)
Arthralgia	21 (35)	Petechiae	37 (62)
Myalgia	20 (33)	Epistaxis	21 (35)
Hepatomegaly	20 (33)	Hermann's rash	13 (22)
Lethargy	4 (7)	Gum bleeding	10 (16)
Ocular pain	3 (5)	Hematemesis/melena	8 (13)
Pleural effusion	3 (5)	Ecchymosis	2 (3)
Tonsillo-pharyngeal congestion	2 (3)		

* 60 confirmed - dengue patients with clinical data

of DHF, were observed in only 37% and 77% of patients, respectively.

DISCUSSION

The present study showed that dengue infection confirmed by virus isolation and or serology was less than 50%, significantly lower than those reported in previous local studies (Tupasi *et al,* 1987; Manaloto *et al,* 1987). Since only laboratory confirmed dengue cases are reported, we believe that the data represent only minimal figures and the true incidence is probably higher. Many serum samples were not appropriate for virus isolation and a large number of patients lack convalescent sera. Proper collection, handling and storage of specimens are crucial considerations in the success of any laboratory diagnosis and that collection of convalescent serum is vital in the interpretation of results using the HI test. These are important information that should be emphasized to physicians. More over, our results also underscore the need to establish laboratory capabilities that would allow diagnosis in time for clinical management as well as disease surveillance.

A majority of patients had a secondary type of antibody response. Halstead proposed that DHF is due to a self destructive host response and some persons are sensitize by their first infection hence the course of a second infection with a different serotype may be altered adversely by the immune response (Halstead *et al,* 1969). Unlike in other countries where secondary infection is associated with dengue shock syndrome (Sumarmo *et al,* 1983; Ungshusak and Kunasol, 1988), in this study and in previous reports from the Philippines (Manaloto *et al,* 1987; Songco *et al,* 1987), most dengue and DHF cases were of secondary type of infection but most often did not progress into a profound shock. The explanation for this is not clear although genetic or biologic factors may be considered. Perhaps the early recognition of the disease by parents and timely and appropriate medical care by physicians contributed to the finding of only a few cases of DSS.

Dengue infection is an acute, mosquito- transmitted viral disease caused by any of four serotypes (1, 2, 3, and 4). Most local studies from 1980's to 1990's had identified only serotypes 1, 2, and 3. Serotypes 2 and 3 were associated with milder manifestations whereas type 1 was associated with DSS, the latter finding, however, is not consistent with observations in this study. An important benefit of effective surveillance is that it can monitor the introduction of a new virus type or a new virus strain which is said to be predictive of an impending epidemic. With this type of information, epidemic transmission can be predicted and an epidemic could be prevented by implementing control measures (Gubler, 1989). In this study, only

type 1 and 2 were isolated, therefore the reintroduction of type 3 or the appearance of type 4 will alert health authorities to start an effective mosquito control measures to avert such epidemic.

The clinical and laboratory findings are similar to reports of previous local studies (Tupasi *et al,* 1987; Manaloto *et al,* 1987; Songco *et al,* 1987). Thrombocytopenia was observed in only 22(37%) and hemoconcentration in 46 (77%) of patients. If the case definition of DHF is strictly followed wherein the four criteria, namely, fever, hemorrhagic tendencies, thrombocytopenia and hemoconcentration must all be present, then only 37% and 77% of the patients fulfilled the criteria and the remainder 38(63%) without thrombocytopenia or 14(23%) without hemoconcentration but with hemorrhagic manifestations (epistaxis, hematemesis, melena or gum bleeding) were classified as dengue fever. This finding supports the need to review the WHO case definition of DHF and revise where necessary. These clinical signs and symptoms in dengue are non-specific, therefore, a laboratory confirmation is important.

It is of interest that the highest incidence occurred among older children and young adults although dengue infection continues to be a significant problem throughout childhood. A ten year observation of dengue cases also reported an increasing proportion occurring in adults (Hadinegoro and Nathin, 1990). This perhaps could be attributed to the transmission of multiple dengue serotypes at relatively low rates of infection and therefore previously uninfected adults could become susceptible to dengue infection.

The effect of age, sex, infecting serotype and type of antibody response was not demonstrated in patients who had DHF Grade III, probably because of the small number of cases. Since there was no mortality, the effect of the above host factors on the outcome of patients could not be evaluated.

To evaluate dengue transmission, an active surveillance system was initiated in four hospitals which relied mainly on hospitalized patients presenting with signs and symptoms compatible with dengue. There were several problems identified during the study: the reluctance of some physicians to get involved in the study, inadequate interval between acute and convalescent samplings since the majority of patients were discharged less than a week (mean duration of 5 days), patients' inability to return to the hospitals for their check-up hence convalescent sera could not be obtained, the incomplete filling out of clinical forms, improper collection and storage of blood specimens and inability to avail of a rapid laboratory diagnostic methods. The study was also limited by lack of personnel to follow-up patients in the community (those who did not visit the hospital for their check-up), because of limited finances as well as the change in residence of some patients. Since surveillance is dependent upon the quality of the data gathered, it is essential therefore, that efforts should be put into correcting these deficiences.

Strengthening a dengue surveillance system is a prerequisite to the establishment of an effective control measures against dengue infection, therefore, there should be a coordinated effort of both government and private health institutions in surveillance activities. Public awareness in the diagnosis, prevention and control of dengue infection should be intensified.

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