

DESCRIPTION OF THE CLINICAL PICTURE OF DENGUE HEMORRHAGIC FEVER/DENGUE SHOCK SYNDROME (DHF/DSS) IN ADULTS¹

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INTRODUCTION

Prior epidemic dengue outbreaks in the United States (1922), South Africa (1927), and Greece (1928) afflicted adult patients who developed hemorrhagic manifestations and shock (1). But since 1954, when dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS) was reported as a new phenomenon in the Philippines (2), it has affected mainly children, and there have only been a few isolated descriptions of the severe picture in adults (3).

For over 30 years, up to 1977, there was no evidence of dengue virus circulation on Cuba; but in that and the following year a classic dengue epidemic occurred that affected a large part of the

Cuban population (4). Then, in the summer of 1981, a major epidemic of DHF/DSS occurred for the first time in Cuba and the Americas. That epidemic struck all age groups, both whites and blacks, and both sexes (5).

The present article describes the clinical manifestations of DHF/DSS in adults on the basis of observations made during the 1981 epidemic. Such clinical description has previously been provided only by isolated reports within our area. It is therefore expected that the description provided here will prove useful to other countries in interpreting the clinical-epidemiologic situation—a situation that, with regard to DHF/DSS, is becoming progressively more complex and dangerous.

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MATERIALS AND METHODS

We examined the clinical histories of patients whose diagnosis upon hospital admission was "hemorrhagic dengue" and who had entered the Calixto García, Salvador Allende, and Enrique Cabrera hospitals in the city of Havana during the DHF/DSS epidemic of 1981. From among those whose histories showed a disease picture appropriate for the study, 200 were selected at random. Efforts were then made to retrospectively confirm that the patients involved had experienced dengue-2 infections and to determine whether they had been previously exposed to dengue-1.

Specifically, sera from these 200 subjects were tested for the presence of antibodies to dengue viruses 1 and 2 by the plaque reduction neutralization method (6). Test sera were deemed positive for dengue-1 or dengue-2 antibodies if they reduced the number of plaques of the respective virus by 50% or more. It was considered that all persons with neutralizing dengue-2 antibodies had been infected during the 1981 epidemic, and that all those with neutralizing antibodies to both viruses had experienced secondary infections. All subjects in whom dengue-2 infection could not be serologically confirmed were excluded from the study.

The remaining 104 subjects, in whom dengue-2 infection was confirmed, came to constitute Group 1. All of these subjects were told about the study's aims and significance, and all agreed voluntarily to be included.

A second study group (Group 2) was composed of 26 adults who had died (out of a total of 57 adult fatalities recorded during the epidemic), these being subjects for whom complete autopsy reports were available and whose clinical histories were considered appropriate for the study. In this group the diagnosis of DHF/DSS was clinical and anatomopathologic. (It should be noted that no other hemorrhagic fever exists in Cuba, and that all the cases involved were reported during the height of the epidemic.)

Because the criteria for defining cases as DHF/DSS have previously been developed only for children, while the aim of the study reported here was to offer the elements needed to diagnose and define clinical cases in adults, we decided to include those subjects with a hospital discharge diagnosis of hemorrhagic dengue who were confirmed serologically to have neutralizing antibodies for dengue-2. Regarding the fatalities, those subjects were included who had a clinical diagnosis of DHF/DSS with anatomopathologic lesions compatible with hemorrhagic dengue and who had died during the epidemic. Naturally, the diagnostic criteria developed by the WHO expert group (7) served as a basis for selection of these latter cases.

It should also be mentioned that a detailed review was made of the two study groups' clinical histories, and that prior personal and family pathologies were recorded. This was done principally to detect clinical signs and symptoms of chronic diseases, and to determine the frequency, sequence of appearance, and duration of such ailments. The distribution of such pathologies among the Group 1 and Group 2 subjects was analyzed in terms of the subjects' age, sex, and race, and also in terms of available clinical laboratory findings.

RESULTS

Of the 104 Group 1 subjects selected for the study, 102 (98%) were found to have had confirmed secondary dengue infections (dengue-1 plus dengue-2).

Age, Sex, and Race

The age distribution of the 104 Group 1 subjects and 26 Group 2 subjects generally conformed to that of Cuba's adult population, there being no evident clustering by age among these adult subjects.

Regarding race (Table 1), 81% of the Group 1 subjects were white, while only 65% of the fatally afflicted Group 2 subjects were white, this latter figure being similar to the percentage of whites among the Cuban population according to the last (1981) census. (Despite the relatively high percentage of whites in the Group 1 study sample, the disease also affected mulattoes and blacks.)

Women accounted for 65% of all the Group 1 subjects (Table 2), a predominance that is statistically significant ($p < 0.05$). Most (62%) of the 26 Group 2 subjects were also women; but, partly because of the group's smaller size, this latter predominance was not statistically significant ($p > 0.05$).

TABLE 2. Proportions of men and women in the two groups studied.

	Group 1		Group 2	
	No.	(%)	No.	(%)
Women	68	(65)	16	(62)
Men	36	(35)	10	(38)
Total	104	(100)	26	(100)

Clinical Picture

From the clinical standpoint, four syndromes were identified—these being general (constitutional manifestations), digestive, hemorrhagic, and shock syndromes. Table 3 shows the percentages of Group 1 and Group 2 subjects with constitutional manifestations. As may be seen, fever, headache, asthenia, and arthralgia predominated in both the nonfatal (Group 1) and fatal (Group 2) cases. Rash was found infrequently in both groups, being especially uncommon in Group 2.

In both groups, symptomatic involvement of the digestive system was characterized by nausea and vomiting (Table 4). Hepatomegaly occurred three

TABLE 1. Racial composition of the two groups studied and the general Cuban population (1981 census).

Race	Group 1		Group 2		General Cuban population (%)
	No.	(%)	No.	(%)	
White	84	(81)	17	(65)	(66)
Mulatto	14	(13)	3	(12)	(22)
Black	6	(6)	6	(23)	(12)

TABLE 3. General (classical) dengue signs and symptoms exhibited by members of the two groups studied.

Signs and symptoms	Group 1		Group 2	
	No.	(%)	No.	(%)
Fever	101	(97)	23	(88)
Headache	80	(77)	14	(54)
Asthenia	60	(58)	17	(65)
Arthralgia	56	(54)	10	(38)
Myalgia	46	(44)	11	(42)
Retroorbital pain	20	(19)	7	(27)
Rash	13	(13)	2	(8)

TABLE 4. Digestive system signs and symptoms found among members of the two groups studied.

Signs and symptoms	Group 1		Group 2	
	No.	(%)	No.	(%)
Nausea and vomiting	74	(71)	21	(81)
Anorexia	28	(27)	4	(15)
Abdominal pain	24	(23)	15	(58)
Diarrhea	15	(14)	6	(23)
Hepatomegaly	11	(11)	9	(35)

times as frequently among the fatal (Group 2) cases as it did among the non-fatal (Group 1) cases. Similarly, abdominal pain apparently afflicted 58% of the Group 2 subjects but only 23% of the Group 1 subjects.

Despite the fact that all the subjects were diagnosed as having hemorrhagic dengue, manifestations of the hemorrhagic syndrome were confirmed in only 90% of the Group 1 patients and 65% of the Group 2 patients (Table 5). The predominant hemorrhagic symptoms in both groups were purpuric manifestations (petechiae, ecchymoses, hematomas). Hematemesis was found in a higher percentage of the subjects dying (Group 2) than of those surviving (Group 1).

Shock syndrome, which was present in all the fatal cases, appeared on the average around the fifth day of the

disease. Appearing at the earliest on the third day and at the latest on the eighth, it was frequently irreversible. Clinically, the shock syndrome was characterized by an increased respiration rate, reduced diuresis, a rapid pulse exhibiting narrow pulse pressure until the pulse disappeared, a decline in arterial blood pressure, distal cyanosis, and lack of any response to symptomatic medication.

Among those dying, both pleural effusion and ascites were confirmed in 8% of the cases. Regarding the Group 1 subjects, systematic radiology was not performed; however, pleural effusion was confirmed radiologically in three of these patients.

TABLE 5. Signs and symptoms of dengue hemorrhagic fever (DHF) found in members of the two groups studied.

Signs and symptoms	Group 1		Group 2	
	No.	(%)	No.	(%)
Purpuric manifestations (petechiae, ecchymoses, hematomas)	57	(55)	10	(38)
Metrorrhagia	30	(44 ^a)	4	(25 ^a)
Hematemesis	15	(14)	9	(35)
Gingivorrhagia	15	(14)	2	(8)
Epistaxis	11	(11)	1	(4)
Hematuria	8	(8)	3	(12)
Melena	5	(5)	1	(4)
Hemoptysis	4	(4)	0	(0)
Enterorrhagia	3	(3)	2	(8)
Otorrhagia	1	(1)	0	(0)

^a Percentage of females only.

Shock preceded death in all of the fatal (Group 2) cases; but it was only classified as posthemorrhagic in half of these cases, since the remainder did not show major accompanying hemorrhagic manifestations. No instances of confirmed shock were found among the Group 1 subjects, whose cases evolved in a satisfactory manner.

Clinical Course of the Disease

Among the Group 1 patients the disease lasted an average of seven days, while the Group 2 patients died, on the average, during the sixth day.

At the outset, the clinical picture among the Group 1 subjects tended to be characterized by fever, headache, asthenia, myalgia, arthralgia, and retroorbital pain (Figure 1). Symptoms involving the digestive system began around the second day and lasted three to four days. The first hemorrhagic manifestations began to appear on the third day.

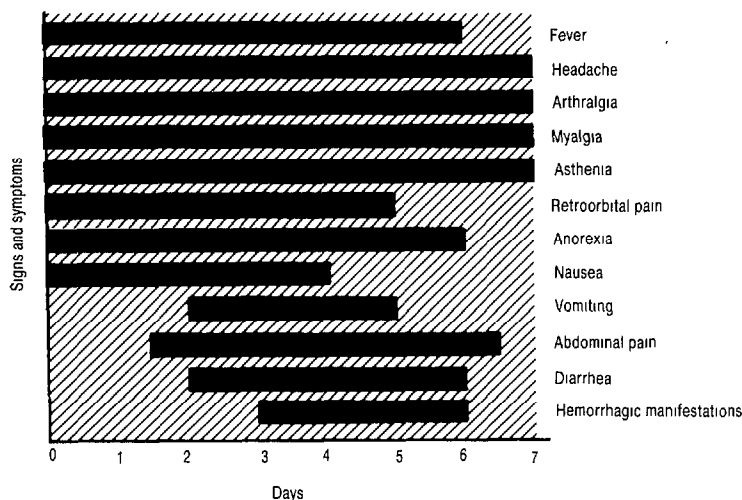
In the fatal cases (Group 2), the initial clinical picture was similar, involving various general and digestive symptoms compatible with classical dengue. Abdominal pain began occurring on the third day, and hemorrhagic manifestations on the fifth, these latter coinciding with the onset of shock and a worsening of the clinical picture that led to death within a few hours.

Clinical Laboratory Results

Platelet counts and hemograms were obtained from all the subjects in a systematic fashion upon their admission to the hospital. If some change in a person's condition was noted, these analyses were repeated every 12 or 24 hours. Hematocrits were not obtained from all of the subjects.

Thrombocytopenia was found in 80.3% of the Group 1 cases and 71.8% of the Group 2 cases. In contrast, hemoconcentration appeared relatively less common in Group 1 than Group 2, being found in 34% of the former cases as compared to 92% of the latter. (It should be noted that besides using laboratory criteria to determine hemoconcen-

FIGURE 1. Clinical course of the disease during days one through seven among the study subjects who recovered (Group 1).



tration we also used clinical criteria, finding hemoconcentration in all subjects who presented clinical, radiologic, or autopsy evidence of a shift of fluid into their body cavities.)

Leukocytosis ($\geq 10,000$ leukocytes per cubic millimeter), with a predominance of neutrophils and lymphopenia, was found more commonly in Group 2 subjects (44%) than in Group 1 subjects (9.3%).

Antecedent Pathologies

Relatively high percentages of the Group 2 subjects were found to have had histories of bronchial asthma (11.5%) and sickle cell anemia (15.3%). In contrast, the prevalences of these diseases among the adult Cuban population were 7% for bronchial asthma and 0.08% for sickle cell anemia. These differences are statistically significant ($p < 0.05$). Diabetes mellitus was also found

relatively frequently among the Group 2 subjects, but the difference between this prevalence and that found in the general Cuban population was not statistically significant.

DISCUSSION AND CONCLUSIONS

Our results show that 98% of the subjects whose cases evolved favorably (those in Group 1) had been infected by both the dengue-1 and dengue-2 viruses. This fact, together with the results of other research carried out by our group that yielded similar results (8, 9), suggests that such secondary infection is a necessary condition (though not the only condition) required for development of hemorrhagic dengue. It also supports what Halstead has postulated regarding the etiopathology of this disease (10).

Among adults, the 1981 hemorrhagic dengue epidemic appeared to afflict all age groups about equally,

the age distribution of the affected adults being similar to that of the Cuban population as a whole (11). In Southeast Asia and the islands of the Western Pacific, the disease is reported to occur primarily among children (people under age 14). This circumstance could relate to the broad, permanent, and sometimes simultaneous circulation of the four dengue virus serotypes in these regions (1)—a circumstance implying that practically the entire population, on reaching adulthood, may already be immune to dengue viruses.

Since Cuba experienced intense circulation of dengue-1 in 1977–1978 (4) and dengue-2 in 1981 (5), it was possible for the disease to arise in children and adults whose only two experiences with these viruses occurred within a four-year period. (As previously noted, there is no evidence of dengue virus circulation in Cuba between 1945, when a limited outbreak occurred in the city of Havana (12) and 1977, when dengue-1 was introduced.)

Recently, Fang et al. (13) reported on the epidemic of DHF/DSS that occurred in Malaysia in 1982, when some 56% of the persons affected were adults. The authors state that the reason for the observed age displacement toward those over 15 “is not clear, but may be due to the immune status of the community in which the virus circulated.”

In Cuba, although DHF/DSS affected whites, mulattoes, and blacks, the highest frequency of cases was found in whites. Bravo et al. (9), in a study of three groups of Cuban patients with DHF/DSS, reports that the disease occurred at a significantly greater rate among whites. White fatalities were not found to predominate in that study, but this could conceivably be explained by the presence in the study group of two black patients with sickle-cell anemia (a genetic condition associated with

blacks), this latter being a risk factor for onset of the severe disease (9). If these two patients were removed from the sample, the percentage of fatalities among whites would exceed the percentage of fatalities among members of other races.

Overall, the work reported here underscores the fact that hemorrhagic dengue is not limited to people of Asian origin, and that whites, mulattoes, and blacks are all susceptible. (In this vein, it is worth noting that initial research results obtained by our group have shown that the phenomenon of immunologic amplification was not found to occur in macrophages from the vast majority of a group of blacks studied—14).

Regarding sex, other authors (1, 3, 15) have reported a relatively high incidence of hemorrhagic dengue among young girls over four years old. In our study women were more frequently affected. These findings can be related to the apparently greater immunocompetence of females (3).

From the clinical standpoint, it should be noted that hepatomegaly, abdominal pain, and hematemesis were relevant signs in fatal cases and could be taken to suggest a poor prognosis. Other authors have made similar reports on afflicted children (16–19).

The hemorrhagic manifestation most frequently observed was purpura, a finding also reported by other authors studying childhood cases (8, 16, 19).

Hematemesis was observed twice as often among the Group 2 fatalities as it was among the Group 1 patients

who evolved favorably. It also appeared before or on the same day that shock emerged, a finding that differs from what has been reported for children (both on Cuba and in Southeast Asia), who have been found to experience bleeding as a terminal picture with some frequency after irreversible shock has been established (7).

Among the Group 1 adults whose cases evolved favorably, shock was not observed. (This finding contrasts sharply with observations made of Cuban children—20, 21.) In general, it can be said that shock was observed less frequently among adults than among children, but that when it appeared in an adult it was more serious and generally led to death. In contrast, shock established in a child often proved reversible, so that relatively few fatalities occurred. This circumstance suggests there may be important differences between the pathogenesis of shock in children and adults; and it may help explain a pattern observed in our region—one involving an increased rate of adult fatalities that is not accompanied by a corresponding increase in severe adult cases (22, 23).

On the basis of our experience, we are able to offer data that appear useful for clinical diagnosis of DHF/DSS in adults. Specifically, a diagnosis of DHF/DSS can be made when the epidemiologic conditions necessary for it are present, and when an individual of any age, race, or sex shows appropriate general manifestations (fever, headache, asthenia, myoarthralgia), gastrointestinal manifestations (nausea, vomiting), minor or major hemorrhagic manifestations, or laboratory evidence of hemoconcentration ($>20\%$ hematocrit increase) and thrombocytopenia ($<100,000$ platelets per cubic millimeter).

For practical purposes, we consider that the epidemiologic criteria must always be met. Regarding the clinical

criteria, we feel at least two general manifestations and one hemorrhagic symptom (or thrombocytopenia) must be present in order to justify the diagnosis.

It should be mentioned that the clinical diagnosis is always presumptive, and that whenever possible serologic or virologic confirmation should be sought. Anatomopathologic data can add confirmatory elements to the diagnosis by verifying the existence of lesions associated with the disease.

Among the most interesting clinical laboratory findings of this investigation were confirmation of thrombocytopenia in a high percentage of the patients, both among those dying and those recovering, and detection of hemoconcentration in only 34% of those recovering but in 92% of those dying. Obviously, the presence of these two disease indicators was not uniform among the study subjects, possibly because of the times when blood samples were taken or because of treatments the patients were receiving. In any case, both severe and fatal cases were seen in which neither thrombocytopenia nor hemoconcentration could be confirmed. However, these findings should not be regarded as reducing the value of these two indicators for DHF/DSS diagnosis, prognostication, and monitoring. Indeed, they are the most important laboratory indicators to keep in mind, especially since thrombocytopenia can substitute for the clinical hemorrhagic manifestation required for diagnosis.

The digestive manifestations are not essential to the clinical diagnosis, but if present they reinforce it.

In our experience, the appearance of thrombocytopenia in a patient who otherwise had only general symptoms determined hospital admission. If hematemesis, abdominal pain, or hepatomegaly appear, the case should be considered grave and should be watched closely. Ultimately, the severity of the clinical picture will depend on the magnitude of the hemorrhagic syndrome and appearance of the shock syndrome.

As previously reported (9, 24), bronchial asthma, diabetes mellitus, and sickle-cell anemia have been identified as discrete risk factors in the groups of adults studied. The mechanisms by which these chronic diseases have a negative impact on the disease's evolution are currently being investigated. At present it appears that these mechanisms may somehow be related to certain characteristics favoring the infection of macrophages in dengue patients.

In cases taking a favorable clinical course the leukogram appears normal, with a differential count showing a predominance of lymphocytes (1). In contrast, the fatal cases that we studied exhibited moderate leukocytosis with neutrophilia and lymphopenia. This observation coincides with what has been reported by other authors (7, 19-25), who state that the leukogram may show variable values, that mild to moderate leukocytosis may be observed, and that this leukocytosis may increase, especially before hemorrhage occurs.

The fatal picture of the disease that we observed was somewhat more prolonged than that described by Nisalak et al. (26) in a study of fatal childhood cases. This latter study found death to occur, on the average, during the fourth or fifth day following the onset of symptoms. Our study found a somewhat different situation, with the clinical picture deteriorating between the third and seventh day, the disease lasting an average of six days among the patients who died and seven days among those who recovered.

Keeping in mind that the criteria adopted by WHO for clinical diagnosis and for classification according to degrees of severity have served as a practical guide in many parts of the world, we consider that these criteria are valid for the adult patient and that their use should be continued. The data provided by this study indicate some evolutionary and clinical peculiarities in the adult patient that should be valid for prospective studies conducted at the time of another DHF/DSS epidemic involving a substantial number of adults. The results presented here are in no way regarded as conclusive, however, because our studies have been retrospective and have been based upon data obtained during the epidemic that were analyzed several years later. Nevertheless, we consider them highly useful, especially in providing information suited to making an effective contribution to future studies.

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SUMMARY

Previous descriptions of dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS) in adults have been limited. This article assesses the disease cases of 130 Cuban adults who became ill during the 1981 dengue epidemic in that country and who were diagnosed as having hemorrhagic dengue. One hundred and four of these subjects (comprising Group 1) were admitted to one of three major Havana hospitals and recovered. The other 26 (comprising Group 2) died. The information cited was obtained from the two groups' clinical histories, serologic testing of the Group 1 subjects, and autopsy reports on the Group 2 subjects.

Age did not appear to be a risk factor among these adult subjects; but race and sex appeared to play a role in the disease, a disproportionate share of both groups being white and female. Classical dengue symptoms (fever, headache, asthenia, myalgia, arthralgia, retroorbital pain, and occasionally rash) predominated in both groups. Digestive symptoms (nausea and vomiting, anorexia, abdominal pain, diarrhea, and hepatomegaly) were also common. Hemorrhagic symptoms were confirmed in 90% and 65% of the Group 1 and Group 2 subjects, respectively, and shock occurred in all the fatal cases.

The study subjects typically developed classical dengue symptoms at the outset, followed by digestive and hemorrhagic symptoms. The Group 1 subjects recovered after an average of seven days of illness. The Group 2 subjects began to show shock symptoms on the fifth or sixth day and a worsening of their condition that led to death in a few hours.

Hemoconcentration and thrombocytopenia (especially the latter) were

found in both groups. Leukocytosis was found in both groups but was more common in Group 2. Antibodies to both dengue-1 and dengue-2 viruses were found in the sera of nearly all (98%) of the Group 1 subjects.

Overall, these and other results (8, 9) suggest that such secondary infection is a necessary condition (though not the only condition) required for development of hemorrhagic dengue. They also suggest that numerous adults were afflicted in 1981 because a large adult population existed that had previously been infected with dengue-1 in 1977-1978 but had never been exposed to dengue-2.

Also, the evidence from this study indicates that shock rarely occurred among the adults who recovered, but that it invariably occurred and led frequently to death in those who died. This constitutes a noteworthy departure from the typical course of DHF/DSS in children, who commonly experience and recover from shock symptoms.

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