BACKGROUND

Halstead, in a review of the literature (1), gives an account of pre-1980 data on dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS) in different parts of the world. Although the pandemic character of this problem was pointed out in earlier works (1), from the 1950s until 1981 it remained confined to South-East Asia, where it affected mainly children.

Following a small outbreak of classical dengue in 1945 (2), no dengue virus activity of any kind was recognized in Cuba until 1977, when an epidemic occurred that was caused by dengue-1 virus (3). This epidemic, characterized by a clinical picture of classical dengue, lasted into 1978; thereafter, dengue-1 remained in circulation with low endemicity (4).

From May to October 1981 another epidemic occurred that was caused by dengue-2 virus. This outbreak caused cases with severe clinical pictures of DHF/DSS (5). In all, 344,303 cases were recorded, including 10,312 that were severe and 158 (101 in children and 57 in adults) that were fatal (6). Although the afflicted included both children and adults, the highest incidence of severe and fatal cases occurred among children four and five years old. No severe or fatal cases occurred among children one or two years old (6).

A campaign to control and eradicate the vector mosquito Aedes aegypti followed on the heels of the outbreak and allowed the disease to be eliminated in a little over four months. Since then the vector house indices have
remained at very low levels (on the order of 0.001), and no clinical cases of dengue have been confirmed since 10 October 1981. This circumstance has facilitated retrospective studies that have provided reliable data.

The work described here examined the clinical picture found in a group of children clinically diagnosed as having DHF/DSS. It also sought to determine whether secondary-type dengue infections in these children placed them at relatively great risk of developing the severe clinical form of the disease.

As far as we know, this is the first well-documented study of the disease in a Caribbean setting and population; hence, it may be considered a starting point for description of DHF/DSS in the region, as well as a source of very useful data for comparison with current information about the disease in other regions.

MATERIALS AND METHODS

The study sample consisted of 124 children diagnosed as having DHF/DSS, grades III and IV, according to the criteria of the WHO Advisory Committee on DHF (7). All of these children were admitted to the Centro Habana and William Soler pediatric hospitals (two large health centers) during the 1981 epidemic. A blood sample was taken from each child in April 1983, 18 months after the epidemic ended, and the child's clinical record was reviewed. The blood was collected by finger-tip puncture on two Nobuto type A filter papers (Toyo Roshi International, Tokyo, Japan). Each sample was dried, placed in a sealed plastic bag, and stored at $-20^\circ$C until antibody tests were performed. The dried blood was then eluted to produce a serum dilution of 1:30 (8).

Each sample was tested for antibodies to dengue-1 and dengue-2 by plaque reduction neutralization using LLCMK2 cells (9). The virus strains employed were isolated in Cuba during the 1977 (dengue-1) and 1981 (dengue-2) epidemics (3, 5). A child was deemed to have a primary infection when the test showed over 50% plaque reduction against only one dengue virus, and a secondary infection when the test showed over 50% plaque reduction against both dengue viruses.

RESULTS

One hundred twenty-two children (98%) were found to have neutralizing antibodies against both dengue-1 and dengue-2. Figure 1 shows the age distribution of the 124 patients studied (it should be emphasized that only one patient was less than 3 years old). The youngest child, who was four months old, exhibited a primary-type antibody response to dengue-2.

The bulk of the study children were four to 11 years old. As Table 1 shows, the group consisted about equally of boys and girls. However, the Table 2 data indicate that 86% of the children were white, 8% were mulatto, and only 6% were black. Comparison of these figures to the ethnic distribution of the Cuban population indicates that the frequency of severe disease was significantly higher among whites ($p<0.01$).
FIGURE 1. The age distribution of the 124 study children with DHF/DSS.

![Age Distribution Chart]

Table 1. Sex distribution of the study children.

<table>
<thead>
<tr>
<th>Sex</th>
<th>No.</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>60</td>
<td>(48)</td>
</tr>
<tr>
<td>F</td>
<td>64</td>
<td>(52)</td>
</tr>
</tbody>
</table>

Regarding the clinical disease symptoms exhibited, fever—either alone or accompanied by other manifestations such as vomiting or nausea—was the most common reason for hospitalization.

The study subjects were generally hospitalized at least 24 hours before shock occurred. (In most cases shock was observed four or five days after the onset of symptoms.) The period of hospitalization ranged from five to 15 days, with most of the children being hospitalized for six to 10 days.

Table 3 shows the main clinical and laboratory findings. Clinically, the children showed high rates of fever, vomiting, and hepatomegaly. Manifestations such as hydrothorax and ascites were frequently found in the children with severe clinical pictures. Thrombocytopenia was observed in 78% of the patients and hemoconcentration in 83%.

Regarding hemorrhagic manifestations (Table 4), these were exhibited by 85 children (68.5% of the study
TABLE 2. Racial distribution of 123 of the study children.\(^a\)

<table>
<thead>
<tr>
<th>Race</th>
<th>Study children</th>
<th>Racial distribution of the general Cuban population(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>106 (86)</td>
<td>(66)</td>
</tr>
<tr>
<td>Mulatto</td>
<td>10 (8)</td>
<td>(21.9)</td>
</tr>
<tr>
<td>Black</td>
<td>7 (6)</td>
<td>(12)</td>
</tr>
<tr>
<td>Asiatic</td>
<td>0 (0)</td>
<td>(0.1)</td>
</tr>
<tr>
<td>Total</td>
<td>123 (100)</td>
<td>(100)</td>
</tr>
</tbody>
</table>

\(^a\) The race of one of the 124 study children was not recorded.

\(^b\) Based on the 1981 census.

TABLE 3. Principal clinical and laboratory findings obtained from examination of the 124 study children.

<table>
<thead>
<tr>
<th>Clinical and laboratory findings</th>
<th>Study children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. / No. positive/examined (%) positive</td>
</tr>
<tr>
<td>Fever ((&gt; 37^\circ \text{C}))</td>
<td>120/124 (97)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>106/124 (87)</td>
</tr>
<tr>
<td>Thrombocytopenia ((\leq 100,000/\text{mm}^3))</td>
<td>97/124 (78)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>83/124 (67)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>78/124 (63)</td>
</tr>
<tr>
<td>Hemorrhagic manifestations</td>
<td>85/124 (68.5)</td>
</tr>
<tr>
<td>Hemocoagulation (increase (\geq 20%))</td>
<td>103/124 (83)</td>
</tr>
<tr>
<td>Ascites</td>
<td>38/124 (31)</td>
</tr>
<tr>
<td>Hydrothorax</td>
<td>70/124 (56)</td>
</tr>
</tbody>
</table>

TABLE 4. The frequency of the various hemorrhagic manifestations found in 85 of the 124 study children.

<table>
<thead>
<tr>
<th>Hemorrhagic manifestations</th>
<th>Study children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. / No. positive/examined (%) positive</td>
</tr>
<tr>
<td>Petechiae</td>
<td>62/124 (50)</td>
</tr>
<tr>
<td>Hematemesis</td>
<td>37/124 (30)</td>
</tr>
<tr>
<td>Melena</td>
<td>10/124 (8)</td>
</tr>
<tr>
<td>Ecchymoses</td>
<td>9/124 (7)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>11/124 (9)</td>
</tr>
</tbody>
</table>

Regarding possible associations with asthma (Table 5), 21.5% of the children were found to have a personal history of asthma, while 36% were found

TABLE 5. The proportions of 88 study children examined who were found to have a personal or family history of asthma.

<table>
<thead>
<tr>
<th>Asthma histories</th>
<th>No.</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal</td>
<td>19</td>
<td>(21.5)</td>
</tr>
<tr>
<td>Family</td>
<td>32</td>
<td>(36)</td>
</tr>
</tbody>
</table>
to have a family history of this ailment. (Asthma is typically found in 11% of the Cuban child population.)

**DISCUSSION AND CONCLUSIONS**

DHF/DSS is observed mainly in South-East Asian and Western Pacific areas where two or more dengue virus serotypes are circulating in an endemic fashion (1). The first studies conducted in Thailand by Nimmanitya et al. (1969) and Halstead et al. (1970) (10, 11) showed that secondary-type infection constituted a risk factor for development of DHF/DSS. However, there were a few reports of severe clinical pictures in patients suffering from primary infections (12, 13).

Because only two dengue virus serotypes have been circulating in Cuba over the last 40 years (during the 1977 and 1981 epidemics) (3, 5), retrospective serologic studies in patients with clinically diagnosed DHF/DSS grades III and IV can help to determine whether or not secondary-type infection was a factor predisposing to severe evolution of the disease in such patients. Of the 124 children with DSS included in this study, all but two yielded a secondary-type antibody response.

Rosen (1982) (14) has pointed out the convenience of comparing the prevalence of primary and secondary antibody responses in Cuban patients who suffered from DHF/DSS with the prevalence to be expected on the basis of the share of the population infected with dengue-1 virus in 1977. In this regard, Cantelar et al. (1981) (15) have reported that after the dengue-1 epidemic, 44.46% of the Cuban population had hemagglutination-inhibition antibodies to dengue virus. If this figure is accepted as valid, then it appears that the percentage of DHF/DSS study subjects with dengue-1 antibodies (98%) was over twice that found in the general population. This finding therefore tends to confirm the importance of pre-existing antibodies as a risk factor. Similarly, Diaz et al. (16) studied a group of 104 adult patients in whom DHF/DSS was diagnosed during the same epidemic; only two patients showed primary-type infections.

It is also important to note that of the 101 fatal DHF/DSS cases in children, no case was found in any child one or two years old. Secondary-type infections would be very difficult to explain in such children, because they were born principally in 1979 or 1980, years when the circulation of dengue-1 virus in Cuba was very low (17).

In a pattern similar to that reported in the literature (18), most of the afflicted study children were four to 11 years old. It also seems relevant to note that severe disease cases were found in adults during this epidemic, an unusual development probably ascribable to the fact that Cuban adults as well as children were susceptible to a second dengue infection (6).

All of this calls attention to the four-month-old infant who was one of the two study subjects with a primary dengue-2 infection. In this case the development of shock could be explained by the presence of passive maternal antibodies (18), although this circumstance could not be confirmed, since it was not possible to take a blood sample from the mother.
The occurrence of four other fatal cases in children under six months old might be explained the same way (this could not be confirmed for lack of blood samples from their mothers). In any event, the occurrence of severe disease during the first six months of life in the Cuban epidemic (6) differs from what has been seen in South-East Asia, where cases typically occur between six and 12 months of life (18).

This difference appears related to maternal antibody titers. In Cuba, where dengue virus circulation has been restricted to two serotypes in two epidemics, the level of maternal antibodies should be lower than the level of maternal antibodies in endemic areas where several dengue virus serotypes are permanently and simultaneously circulating. Hence, antibody levels appropriate for contracting dengue and developing severe symptoms could have been reached in our newborns at an age several months younger than that when those same levels were reached in children from endemic areas of South-East Asia and the Western Pacific Islands.

A preponderance of DHF/DSS in females over four years old has been documented by Halstead (1, 18). This preponderance had been ascribed to a stronger immunologic response among females than among males. No such preponderance was seen in our study, however, the numbers of boys and girls with severe symptoms being about equal. Similarly, no female preponderance was found by Martínez et al. (1984) (19) among 249 children admitted to the William Soler Hospital with DHF/DSS during the 1981 epidemic, nor was any found among the 101 children who died of DHF/DSS (6).

It is of course possible that social practices or other factors could produce greater exposure to the virus among girls over four years old in the areas with endemic DHF/DSS. Such exposure could explain the higher prevalence of the disease among females in this age group.

Although it has not been possible to correlate DHF/DSS with racial factors, it had been known that the prevalence of dengue infection among non-natives is much lower than the prevalence among natives in South-East Asia (1). However, this has been correlated with less exposure of the non-native population to the Aedes aegypti vector. Furthermore, it had not been possible to report on severe disease patterns among whites and blacks (although a 1967 report by Russell et al. (20) described a fatal DHF/DSS case in a white U.S. child), because severe cases were generally restricted to areas where those racial groups are scarce.

In our study, the preponderance of DHF/DSS cases in white children was found to be statistically significant when compared to the ethnic distribution of the Cuban population at large. This pattern, which parallels that found in both adult patients and subjects with fatal cases (21), indicates that the white race might be especially susceptible.

Conversely, in black populations the frequency of DHF/DSS was much lower than what would have been expected. At present there are no findings that rule out the possibility that the black race may exhibit a certain resistance to the disease. In Africa, dengue epidemics are infrequent, although the virus is quite frequently isolated from vectors (22, 23).
Studies conducted in our laboratory (24) have demonstrated a faster multiplication of dengue-2 virus in cultures of human peripheral blood monocytes from white donors when these were treated with subneutralizing concentrations of antibodies.

Halstead (1979) (25) has said that microbial stimuli such as those indicated by a history of previous infections, chronic disease, and metabolic disorders would play a significant role in enhancing dengue infection in man. Among our group of DHF/DSS patients, a personal or family history of bronchial asthma was found at a significantly higher frequency than it was found among the child population at large. In addition, it has been found that diabetes mellitus was a risk factor for development of fatal DHF/DSS cases among Cuban adults (6). These and other as yet unidentified risk factors are also likely to be present in South-East Asia and the Western Pacific Islands.

In this regard, it is important to note the results obtained by Wiharta et al. (26), who demonstrated increased dengue virus multiplication in cultures of human peripheral blood monocytes when these were pretreated with bacterial or parasitic components. This rate of multiplication was higher when subneutralizing concentrations of dengue virus antibodies were added to the cultures. This suggests that parasitic or bacterial infections, along with secondary-type dengue infection, could increase the risk of developing severe symptoms. Study of this matter in areas with endemic DHF/DSS would be of interest.

Following sudden onset with fever and vomiting in the 1981 epidemic, shock typically occurred on the fourth or fifth day of the disease—being preceded in many cases by abdominal pain and petechiae. Contrary to what was observed in adults (16), the presence of shock in children did not usually lead to a fatal outcome when rapid and appropriate treatment was applied (27, 28).

In general, the laboratory data and hemorrhagic manifestations found among our study children were similar to those found among 13 children with fatal DHF/DSS during the epidemic (29), although the symptoms were more marked among the latter. Among other things, 92% of the children with fatal cases had upper digestive bleeding, and all of them had thrombocytopenia and hemoconcentration.

The WHO Technical Advisory Committee on Dengue Hemorrhagic Fever (7) includes among the diagnostic criteria for DHF/DSS the presence of thrombocytopenia (equal to or lower than 100,000/mm$^3$) with concurrent hemoconcentration (an increase of 20% or more). However, our study found that thrombocytopenia and hemoconcentration were not reported in 22% and 17% of the patients, respectively. This could have been due to the early treatment established for our patients—most of whom were hospitalized 24 hours before shock occurred—or to procurement of laboratory blood samples after normal platelet and hematocrit levels had been restored.

In general, different authors (9, 30) agree that the most altered figures of both parameters are produced in the most seriously ill patients, particularly in those who die. During the 1973 epidemic in Malaysia, Wallace et al. (31) reported thrombocytopenia in 92.6% of the patients studied and hemoconcentration in 40%. Similarly, George et al. (1971) (30) reported thrombocytopenia below 150,000/mm$^3$.
in 87.5% of a group of study children with DHF. In 72 fatal cases reported in children during the Cuban epidemic, thrombocytopenia was documented in 97% of the cases and hemoconcentration in 96% (32).

All patients in whom severe disease was suspected were hospitalized early. This measure permitted early and appropriate treatment, and also made it possible to learn about clinical evolution of the condition. In general, this early hospitalization, combined with intensive treatment, made it possible to keep the number of fatal cases to a minimum.

In general, where cases had a fatal outcome appropriate measures taken to prevent or control shock were not as successful as expected. In these cases, homeostatic changes appeared so rapid and profound that it was not possible to save the patient.

ACKNOWLEDGMENT

The authors are grateful for the assistance and advice of Professor S. B. Halstead.

SUMMARY

A study was made of 124 children afflicted with dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS) grades III and IV during the 1981 dengue-2 epidemic in Cuba. Nearly all (98%) of these children yielded a secondary-type serologic response to the neutralization test, indicating prior dengue-1 infection. The composition of the study group indicated that children between four and 11 years old were those most likely to be afflicted with severe symptoms.

No predilection for boys or girls emerged, but white children appeared significantly more likely than black or mulatto children to develop DHF/DSS.

In most cases, shock occurred four to five days after the initial onset of symptoms, often being preceded by abdominal pain. Fever, vomiting, and hepatomegaly were the clinical manifestations most commonly found among the study children. Hemorrhagic manifestations were found in 85 (68.5%) of the study children, petechiae and hematemesis being predominant. An unusually large percentage of the study children (21.5%) were found to have a personal history of asthma.

In general, the study findings tended to confirm that infection with dengue-1 some time before infection with dengue-2 was closely linked to development of DHF/DSS. Also, the percentage of study children with a history of asthma supports the theory that this and other sorts of antigenic stimuli can increase the risk of developing DHF/DSS.

The roughly equal sex ratio of the study children contrasted with a female predominance observed elsewhere among children with severe symptoms. This suggests that the latter predominance could be due to social behavior patterns rather than to differences in the immune responses of boys and girls. At the same time, the fact that most of the study children were white suggests that whites may be more likely than blacks to develop severe symptoms.
REFERENCES


16 Díaz, A. Pedro Kouri Institute of Tropical Medicine, Havana, Cuba. Personal communication, 1985.


24 Morier, I. Pedro Kouri Institute of Tropical Medicine, Havana, Cuba. Personal communication, 1986.


