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Why dengue haemorrhagic fever in Cuba? I. Individual risk factors for dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS)

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Abstract

During the dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS) epidemic in Cuba in 1981, we identified some individual risk factors for the development of the severe clinical picture or for the fatal outcome of the disease. The percentage of secondary infection in 3 groups of patients with DHF/DSS was between 95 and 98·3 and it is concluded that secondary infection is an important, but not the only, condition for the development of DHF/DSS. An analysis of these 3 groups of patients and a fourth group of fatal cases showed that chronic diseases such as bronchial asthma, diabetes mellitus and sickle cell anaemia were additional risk factors contributing significantly to the development of DHF/DSS. The study also revealed that race was an individual risk factor, since DHF/DSS was more prevalent in white than in black persons.

Introduction

Dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS) is an extreme and severe manifestation of classical dengue and two main hypotheses have been proposed to explain its development. The first suggests that viral virulence may vary in different strains of the 4 dengue virus serotypes and that DHF/DSS cases may be exceptional dengue infections caused by virulents strains (ROSEN, 1977). The second hypothesis, proposed by HALSTEAD (1970, 1981), is widely accepted; it states that double or sequential dengue infections explain the aetiopathogenesis of the disease; this hypothesis is based on the fact that DHF/DSS occurs in persons with antibodies (actively or passively acquired) to a dengue serotype, which in the presence of a second infecting serotype form infectious immune complexes. Experimental evidence for this, and an explanation of how antibodies mediate the development of DHF/DSS, were provided by HALSTEAD (1979, 1982) while epidemiological evidence in support of the secondary infection hypothesis was provided by WINTER *et al.* (1968) for Bangkok.

The epidemiological aspects in Cuba allow the study of these two hypotheses and permit their evaluation in a well defined situation.

In spite of the wide circulation of dengue virus types 1, 2 and 3 in the Caribbean region, outbreaks of DHF/DSS were not known in the region, though there have been reports of isolated cases with haemorrhagic manifestations in Puerto Rico and Jamaica (LÓPEZ-CORREA *et al.*, 1978; FRASER *et al.*, 1978). In 1977 an epidemic of Dengue 1 occurred in Cuba (MAS, 1979). It was characterized by a mild clinical picture, and over 500 000 persons were affected. It appeared after more than 30 years during which there was no apparent viral circulation on the island. An epidemic of DHF/DSS in 1981 caused by dengue 2 virus affected over 300 000 persons in the country, causing 10 000 reported severe cases and 158 deaths (KOURI *et al.*, 1983). The first cases were seen in May and by 10 October, following an intensive vector control campaign which is still maintained, the epidemic was over.

The epidemiological situation in Cuba was unique since a population almost totally susceptible to dengue virus suffered 2 large epidemics by dengue virus types 1 and 2 in 4 years, the second epidemic being characterized by haemorrhagic fever and shock. During the second epidemic certain individual risk factors were identified, which appeared to influence the severity of the clinical picture, and its eventual outcome. In this paper we present these individual risk factors as well as the epidemiological evidence for their role in DHF/DSS.

Materials and Methods

In order to identify the possible risk factors for DHF/DSS, we studied 4 groups of patients; (1) the clinical charts of 98 fatal cases (72 children and 26 adults) clinically and pathologically diagnosed as DHF/DSS; (2) 103 patients of DHF/DSS grades II and III as classified by the World Health Organization expert committee for the study of dengue haemorrhagic fever (WHO, 1980); (3) 124 children with DSS (Grades III and IV) and (4) 104 adults with DHF (Grade II) who had a favourable evolution. In the last 3 groups the diagnosis was confirmed serologically by haemagglutination inhibition (HI) and neutralization (N) tests for antibodies to dengue virus types 1 and 2.

The data were subjected to the chi-square test with Yates correction for continuity (SNEDECOR & COCHRAN, 1973).

Results

The following individual risk factors were identified: secondary character of the infection; chronic diseases, including bronchial asthma, diabetes mellitus and sickle cell anaemia; and being of the white race.

Secondary character of the infection

We studied 3 groups of patients clinically diagnosed as DHF/DDS. The first group (GUZMÁN *et al.*, 1984a,b) was composed of 103 patients (children and adults) admitted to hospital with a clinical diagnosis of DHF, grades II and III, who were serologically confirmed by testing paired sera by the HI test. Of

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Table 1—Type of infection in 3 groups of patients with DHF/DSS

	Group I* (Patients with DHF/DSS)		Group II** (Children with DSS)		Group III** (Adults with DHF)	
	No.	%	No.	%	No.	%
Primary infection	5	5	2	1·5	2	2
Secondary infection	98	95	122	98·5	102	98
Total	103	100	124	100·0	104	100

*Detection of HI antibodies
**Detection of N antibodies

these patients, 5 (5%) were primary infections and 98 (95%) were secondary infections (Table 1); 91% of the cases of secondary infection had some haemorrhagic manifestations; 20 patients presented shock and among these only one had a primary infection.

The second group consisted of 124 children under 14 years of age admitted to hospital with DSS (grades III and IV), and the third of 104 adult patients, with DHF (grade II); neutralizing antibodies were present in all these patients.

It can be seen from Table 1 that only 2 (1·6%) children with DSS were primary infections and 125 (98·3%) were secondary infections. Two (2%) of the 104 adult patients were primary infections and 102 (98%) secondary infections. No seriously ill or fatal case was observed in children aged 1 and 2, who were born after the 1977 dengue 1 outbreak. Figs 1 and 2 show the age distributions of fatal cases in children and of children from 2 big hospitals who suffered from DSS but did not die.

Chronic diseases as risk factors

Chronic diseases have been suggested as possible risk factors for DHF/DSS in southeast Asia (HALSTEAD, 1979). We identified bronchial asthma, sickle cell anaemia and possibly diabetes mellitus as individual risk factors for the occurrence of the severe clinical form of the disease.

Bronchial asthma was frequently found as a personal and/or family antecedent in DHF/DSS cases.

The proportion of fatal cases in children and adults

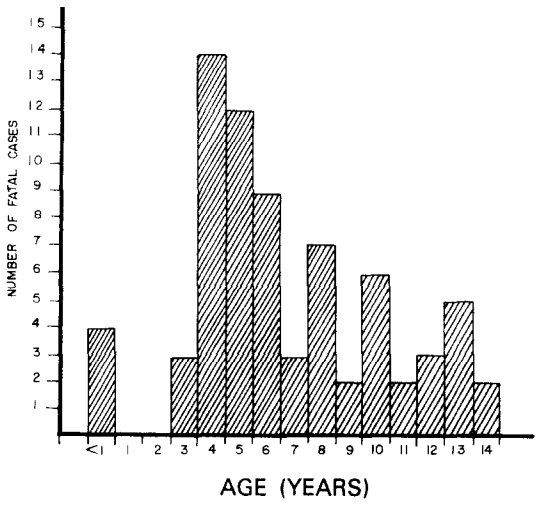

Fig. 1. Age distribution of fatal cases in children.

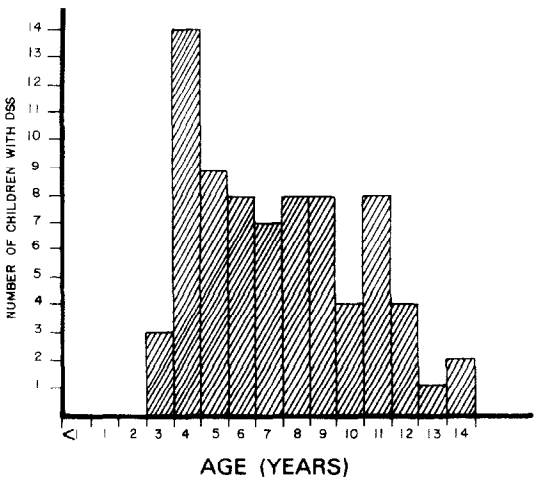

Fig. 2. Age distribution of children with DSS.

Table 2—Bronchial asthma in four groups of patients with DHF/DSS and in the general Cuban population

Patients*		General population
Children with DSS	19/76 (25) a	11% b
Children, fatal cases	16/71 (23)** a	11% b
Adults with favourable outcome	7/104 (7) c	7% c
Adults, fatal cases	3/23 (13)***d	7% c

*Patients with previous history/total of patients (%).
**In one case data were not recorded.
***In 3 cases data were not recorded.
Figures followed by different letters are significantly different.

with bronchial asthma was double that reported in the Cuban population, according to the 1983 national survey on bronchial asthma prevalence rate (RODRIGUEZ DE LA VEGA *et al.*, 1983). The figure for non-fatal cases in children also was double the figure reported in the Cuban child population: all these differences were statistically significant ($P<0·01$). Non-fatal adult cases of DHF developed a mild clinical disease and no difference was seen between the percentage of bronchial asthma in this group and the one in the population.

Diabetes mellitus. One of 23 (4%) of adult fatal DHF/DSS cases suffered from diabetes mellitus. Diabetes was observed in only 2 of 104 (2%) adults who evolved satisfactorily. Taking the prevalence rate of diabetes in the population as 1% (MATEO DE ACOSTA *et al.*, 1973), the observed percentage was

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double in those cases with a favourable outcome and increased fourfold in adult fatal cases: these figures however are not statistically significant.

No personal antecedent of diabetes mellitus was reported in severe or fatal DHF/DSS in children.

Sickle cell anaemia was frequently observed in DHF/DSS cases and the percentage figure for fatal cases in children and adults was significantly ($P<0{\cdot}01$) higher than that for the Cuban population (Martinez Antuña, personal communication). No sickle cell anaemia case was identified among children with DSS or adults who had a favourable clinical evolution.

Race as a risk factor

The high frequency of the severe disease in whites was a constant observation during the 1981 epidemic, and was confirmed by subsequent epidemiological investigations conducted by our Institute (GUZMÁN *et al.*, 1984a,b).

Table 4 shows that the percentages of people of the white race in all four groups of patients were around 80, compared to 66% of whites in the Cuban population based on the 1981 national census; these figures are statistically significant ($P<0{\cdot}05$). The figures for persons of mixed race (mulattoes) were in between. For one black person in the Cuban population there were 5·5 whites and 1·8 mulattoes; the corresponding figures for DHF/DSS cases (children and adults) were 1:19·5:4·5; for children and adult fatal cases, 1:20:3; for children with DSS, 1:14·3:1·3; and for adults (grade II), 1:13·5:2·2. The higher incidence of the severe disease in whites compared to blacks was statistically significant ($P<0{\cdot}05$).

Table 3—Sickle cell anaemia in four groups of patients with DHF/DSS and in the general Cuban population

Patients*		General population
Children with DSS	0 a	0·08% a
Children, fatal cases	4/71 (6)** b	0·08% a
Adults with favourable outcome	0 a	0·08% a
Adults, fatal cases	4/23 (17)***b	0·08% a

*Patients with previous history/total of patients (%).
**In 1 case data were not recorded.
***In 3 cases data were not recorded.
Figures followed by different letters are significantly different.

Discussion

WOODALL *et al.* (1981), discussing the reasons for the absence of epidemics of DHF/DSS from the American region, gave as possible explanations the low virulence of circulating dengue strains, the inappropriate sequence of serotypes, or the time span between two infections. They concluded that should HALSTEAD's (1970, 1981) hypothesis be true, an epidemic of dengue 2 within a 5-year period would be a disaster for the region, considering that, in Puerto Rico alone, over half a million children under age 15 were immune to dengue virus type 1.

This epidemiological situation was present in Cuba, in which 44·5% of the urban population had HI antibodies to dengue virus in 1978 (CANTELAR *et al.*, 1981), evidence for high circulation of dengue virus type 1 during the 1977 epidemic. 4 years later, a second major epidemic due to dengue 2 occurred. SANGKAWIBHA *et al.* (1984) have pointed out that the sequence dengue 1-dengue 2 (the sequence in Cuba) carried the highest risk of occurrence of DHF/DSS; thus the disaster predicted by WOODALL *et al.* (1981) became a reality in Cuba.

ROSEN (1982) stated that the 1981 epidemic of DHF in Cuba offered a unique opportunity to solve the problem of the risk of sequential infection. He pointed out that "it should be relatively simple, even in retrospect, to compare the prevalence of primary and secondary antibody response in the surviving DSS patients, with what would have been expected on the basis of the proportion of the population previously known to have been infected with dengue type 1 in 1977".

Considering that, in 1978, 44·5% of the urban population was immune to dengue 1 (CANTELAR *et al.*, 1981) it would be expected that in the groups studied no more than this percentage would develop secondary infection, if sequential infection were not a risk factor for DHF. In the 3 groups of seriously ill patients (both children and adults), the percentage of secondary infection was between 95 and 98·5, which is highly significant ($P<0{\cdot}01$) compared to the percentage of secondary infection which would be expected in the population.

The absence of fatal and severe cases from the one and 2 year old age groups is an important epidemiological observation, so far not reported in other epidemics. It supports Halstead's hypothesis of secondary-type infection, because this group alone of those

Table 4—DHF/DSS in different racial groups and the composition of Cuba's population according to race

Race	DHF/DSS cases studied during the epidemic (103)	Children fatal cases (72)	Adult fatal cases (26)*	Children with DSS (retrospective study) (124)	DHF adult patients (retrospective study) (104)	Cuban population**
	(%)	(%)	(%)	(%)	(%)	(%)
White	78 b	86 b	77 a	86 b	81 b	66 a
Mulatto	18	11	14	7	13	21·9
Black	4 d	3 d	9 c	7 d	6 d	12 c

*4 adult fatal cases in blacks had sickle cell anaemia and have been excluded from the analysis.
**0·1% Asians.
Figures followed by different letters are significantly different.

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exposed to infection during the 1981 epidemic had no possibility of secondary-type infection. Children less than one year old, also born after 1977, could, however, have maternal antibodies which would enhance the primary infection and result in severe disease.

The data reported in the literature, and our findings, indicate that sequential infection plays an important role in the development of DHF, acting as a risk factor. But it has to be emphasized that it is not the only factor, given the large number of persons who, having suffered a secondary infection, do not present the severe clinical picture. While secondary infection explained the development of haemorrhagic episodes in most of our cases, there was a limited number of patients who had antibodies to dengue 2 only; this implies that there must be some other host-related factor(s) which determine whether an individual suffers from DHF/DSS or not.

Chronic diseases have been suggested as possible risk factors for the development of DHF/DSS, but the occurrence of bronchial asthma, sickle cell anaemia and possibly diabetes mellitus with a high frequency in severe or fatal cases of DHF/DSS has not been reported before.

The mechanism by which these diseases influence the severity of the clinical picture is, so far, unknown. It had been said that "the more immunocompetent the individual, the more severe the shock syndrome" (HALSTEAD, 1979). In asthmatic patients with their component of hyperreactivity and frequent cardiopulmonary lesions, a disease like DHF/DSS, which has a known immunological basis, must express a more severe clinical picture.

In our studies, the percentage of diabetes mellitus in adults was higher than in the general Cuban population. This situation was not observed in children, which is natural as usually this disease is expressed later in life. In Cuba, according to the census of diabetic children, a prevalence rate of 0·14 per 1000 was confirmed (DIAZ *et al.*, 1983). This low prevalence rate would influence the non-identification of diabetes mellitus as a risk factor in childhood.

In other studies conducted by our group, we found that 24% of the fatal cases in children had a family history of diabetes. If we take into account the genetic character of this disease, we can say that some of the 24% of the fatal cases, had they survived to adulthood, would have been confirmed as diabetes patients.

Sickle cell anaemia was found more frequently in severe cases of dengue haemorrhagic fever. This is not surprising when we consider that this is a disease of the blood which would exacerbate the haemorrhagic manifestations of DHF/DSS. In sickle cell anaemia patients who died of DHF/DSS, the disease ran a shorter course than in the rest of the fatal cases, 50% dying in less than 24 h. Of the 8 sickle cell anaemia fatal cases, 5 (63%) presented a preponderance of haemorrhagic manifestations and 3 (37%) of shock.

In fatal and severe cases of DHF/DSS, the percentage of these genetically controlled diseases was generally higher than that observed in the general population. The implication of the chronic diseases mentioned above as risk factors supports the thesis that some genetic factor might play a part in the development of the most severe clinical pictures of dengue haemorrhagic fever. Other diseases are likely to act as risk factors in other countries.

Race was an important risk factor. The frequency with which DHF/DSS occurred in whites was significantly higher ($P<0·05$) than expected from the racial structure of the Cuban population. So far, we do not have an explanation for the high frequency of DHF/DSS in whites. More research is needed to determine whether this is due to the white race behaving as an individual risk factor or if it is because the black race has a certain degree of resistance to DHF/DSS.

It will be necessary to confirm the role of the above-mentioned risk factors and to search for other individual risk factors, in countries where DHF/DSS occurs.

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