HISTAMINE CONTENT IN 24-HOUR URINE IN PATIENTS WITH DENGUE HAEMORRHAGIC FEVER

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INTRODUCTION

Dengue haemorrhagic fever (DHF) is still a serious pediatric problem in Thailand and in other Southeast Asian countries (Udomsakdi, 1973). The present concepts indicate that immunologic mechanism plays a major role in pathogenesis of the disease (Russell, 1971). The immune complex reaction has been postulated for the mechanism of dengue shock syndrome (DSS) (Halstead, 1970, Russell, 1971) by the evidence of the rapid disappearance of dengue virus from the blood and tissue of the DHF patients (Nisalak *et al.*, 1970; Bhamarapravati and Boonyapakvanik, 1966); dengue antibody responses (Ig G) in most of severe cases being compatible with secondary infection(Halstead *et al.*, 1970) and marked reduction of serum complement during the shock phase of illness indicating complement utilization (Russell *et al.*, 1969; Suvatte *et al.*, 1973).

Precise knowledge of mechanism of shock, especially the role of mediators, provides not only better understanding of the pathogenesis of DSS but also provides a more proper treatment of the patients. The present work was conducted to study the role of histamine in DHF and to determine whether this substance is released during the course of the disease.

MATERIALS AND METHODS

The subjects include 12 normal children as a control group, there were 7 males and 5 females. Age ranged from 4-12 years. Patients with DHF who were diagnosed clinically and confirmed by serology include 12 cases. Five were males and 7 were females, and age range from 5-11 years. The severity of DHF were classified as previously described (Phitaksphraiwan *et al.*, 1961). In this study, there were 2 cases of grade I, 4 cases of grade II, 5 cases of grade III and 1 case of grade IV. Serum C_3 were measured in all patients on admission.

Twenty four hours urine of normal subjects and DHF patients were collected in the bottles with 2N.HCl and refrigerated until analysed. The amount of free and total histamine in 24 hours urine were extracted by ion-exchange-Amberlite I.R.C. 50 column chromatography (Bergström and Hansson, 1951), and then measured by four-point bio-assay method (Perry, 1970).

RESULTS

Serological study of DHF patients revealed 3 cases compatible with primary dengue infections and 9 cases compatible with secondary dengue infections.

Serum C_3 of each patient in this study are plotted, compared to the mean levels of C_3 in normal children and DHF in each grade of severity as reported by Suvatte (1973) and shown in Fig. 1.

The values of free and total histamine in normal subjects and patients (expressed as μg of histamine/kg body weight/24 hour urine) are shown in Table 1. The mean values of free and total histamine in normal subjects and patients with student 't' test between both groups are summarized in Table 2.

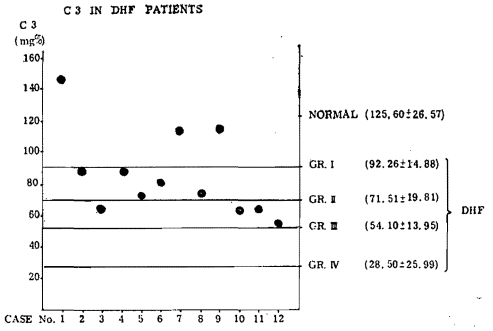

Fig. 1—Serum C_3 in each patient.

Fig. 2 shows the correlation between urinary histamine and severity of the disease. It was found that the mean values of urinary histamine definitely increased with severity of the disease.

DISCUSSION

Previous studies have demonstrated that during the shock phase of DHF, the haematocrit rises sharply (Tuchinda, 1973) and the plasma volume is markedly reduced (Suwanik *et al.*, 1967). Moreover, there are considerable amount of fluid in various serous spaces in

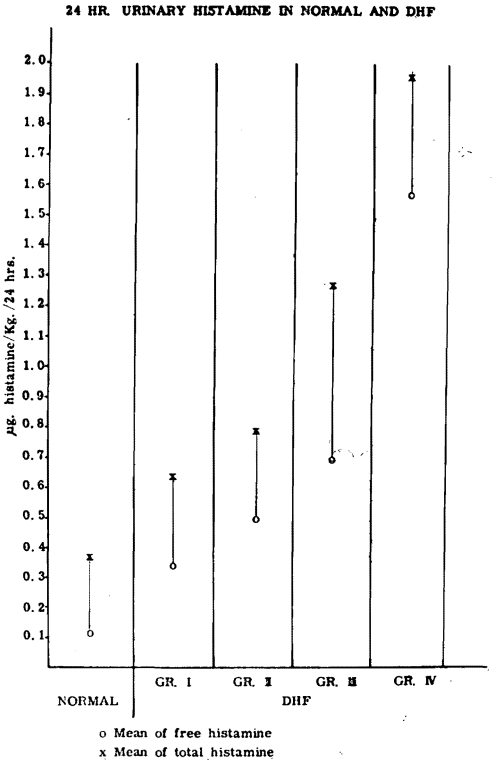

Fig. 2—The mean values of free and total histamine in normal subjects and DHF in each grade of severity.

Table 1

A 24-hour urinary histamine in normal subjects and DHF patients (μg/kg/24 hrs).

Subject	Normal		DHF	
	Free	Total	Free	Total
1	0.0410	0.2460	0.0276	-
2	0.3030	0.6460	0.2444	0.4693
3	0.1010	0.3830	0.4070	1.039
4	0.0660	0.4190	2.1699	-
5	0.0790	0.4740	0.6302	0.7557
6	0.4983	0.6704	0.5200	1.2574
7	0.0740	0.1380	0.4667	0.8078
8	0.0840	0.5820	1.5357	1.9173
9	0.1881	0.6681	0.1930	0.4953
10	0.0271	0.0350	0.2857	0.4018
11	0.0031	0.0839	0.1907	0.4808
12	0.0118	0.1159	1.4624	1.6424

Table 2

Urinary histamine in normal and DHF.

Histamine (μg/kg/24 hrs)	Normal (Mean ± S.D.)	DHF (Mean ± S.D.)	P
Free	0.1230 ± 0.1442	0.6777 ± 0.6714	<0.02
Total	0.3714 ± 0.2418	0.9266 ± 0.5300	<0.01

fatal cases (Bhamarapravati *et al.*, 1967). These findings are strongly suggestive of leakage of intravascular fluid to extravascular spaces in DSS. Mediators released during the shock phase may play a role for increased vascular permeability. Previous study of plasma kinin system failed to provide the evidence of its significant role in the immunopathogenesis of DHF (Edelman *et al.*, 1974).

The results of this study clearly demonstrated that urinary histamine content is much more in patients with DHF than in the normal subjects. Furthermore, more histamine in urine were found in more severe cases. The more urinary histamine should reflect more histamine released in the blood in DHF than in normal subjects. The reasons of increased histamine in DHF is probably due to two mechanisms : firstly during complement activation in DHF, one of the products of C_{3a} or C_{5a} by either classical or alternate pathway or both namely "anaphylatoxin" is released. This substance has three distinct actions : contraction of smooth muscle, increased vascular permeability, and release of histamine from the mast cells, and secondly the increased histamine may be due to the release reaction of the damaged platelets, as the platelet kinetic study by Mitrakul and associates (1974) indicated increased platelet destruction in DHF.

SUMMARY

Twenty-four hour urinary histamine in 12 patients with DHF compared to 12 normal subjects in the comparable age and sex were studied. The results revealed significantly increased urinary excretion in patients with DHF than in normal subjects in both free and total forms. This finding suggests that histamine may be one, if not all, of the mediators released during the course of the disease, especially in the severe cases. Histamine may play an important role for the leakage of intravascular fluid to the various serous spaces resulting in hypovolemia and shock.

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