

IMMUNOLOGICAL ASPECT AND COMPLEMENT IN THAI HEMORRHAGIC FEVER

Vinai Suvatte, M.D., Ph.D.*

Shock and massive hemorrhage are the leading causes of death in Thai hemorrhagic fever (THF)(1,2,3.). From the pathophysiologic studies, it was concluded that shock in THF is due to hemoconcentration and decreased plasma volume which was resulted from the leakage of plasma into extravascular space(4) through the damage capillaries. The causes of hemorrhagic phenomena in THF are

capillary damage, thrombocytopenia, and decreased clotting factors I, II, V, VII, IX, X, of which are in part secondary to liver damage(5,6,7). However, the mechanism for the damage of capillaries, platelets and liver is still not known. The observation that shock in THF is mostly associated with dengue virus infection rather than chikungunya virus(8), raised the possibility that dengue virus

THE RELATION OF DENGUE VIRUS ISOLATION & ANTIBODY RESPONSE IN T.H.F.

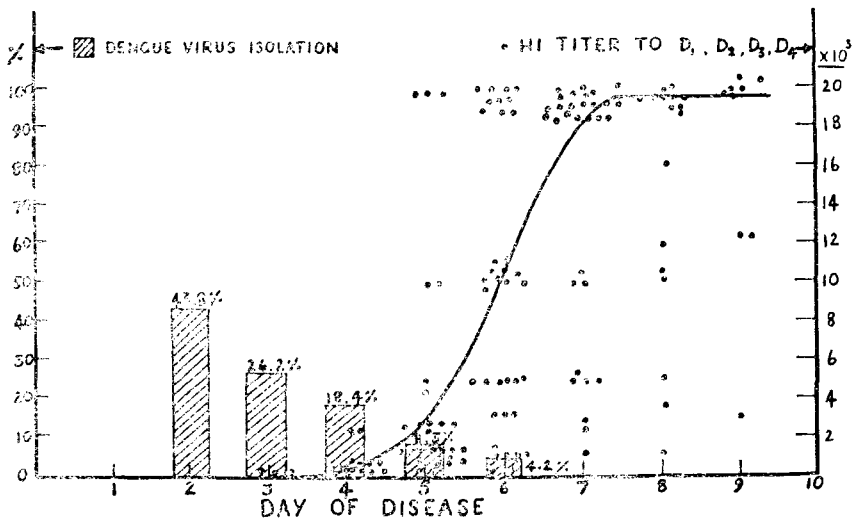


Figure I The relation of dengue virus isolation and antibody response in Thai hemorrhagic fever (T.H.F.). The cross bars represent percentages of dengue virus isolation from the plasma of T.H.F. patients(9). represents serial reciprocal-hemagglutination inhibition (H.I.) titers to dengue type 1, 2, 3 and 4 from 12 T.H.F. patients plotted against day of disease. The solid line represents the approximation of the pattern of increasing HI titers in majority of cases.

* Department of Pediatrics Siriraj Hospital, Mahidol University, Bangkok, Thailand.

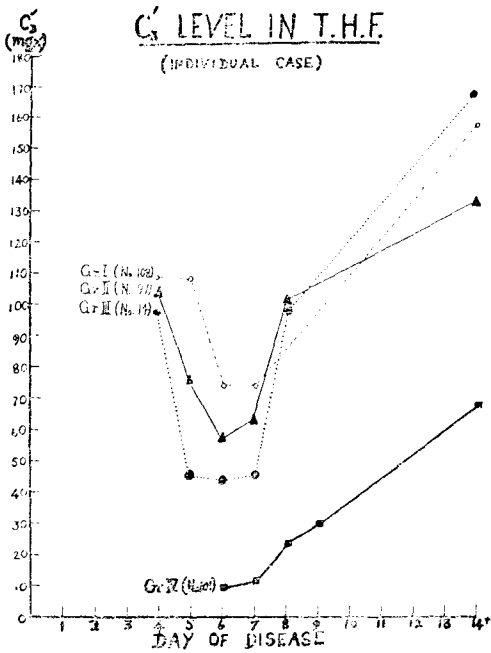


Figure 2. Examples of the serial C3 concentration (mg %) in T.H.F. patients in grade I, II, III and IV as plotted against the day of disease.

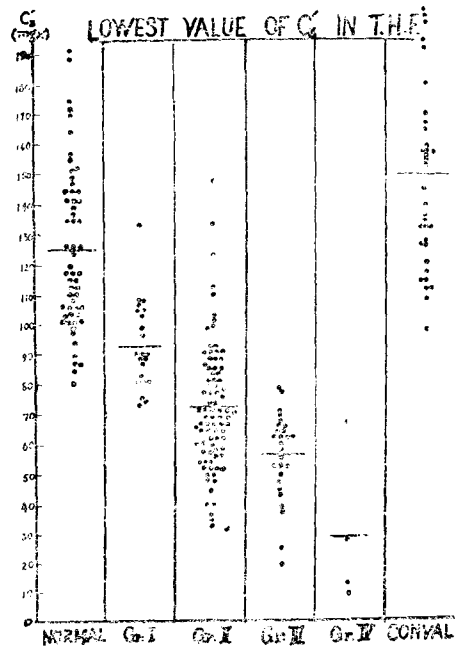


Figure 3. Scattogram of the C3 value (mg %) in normal Thai children and the lowest C3 level from each patient with T.H.F. in grade I, II, III, IV and in convalescent period (day 14+). represents the mean in each group.

may directly cause severe tissue damage seen in THF. However, the findings that dengue virus disappeared rapidly from the blood⁽⁹⁾ as well as from the tissues of THF patients,^(10,11) cast some doubt on the direct tissue damage by dengue virus. When antibody response in THF was studied, it was found that majority of shock cases in THF had secondary dengue antibody response i.e. rapid increase antibody titer within 4-5 days of illness, convalescent antibody titer higher than acute serum titer four fold or over, and the antibody is IgG type^(12,13,15). The relation of dengue virus recovery⁽⁹⁾ and the antibody response in THF patients is shown in Figure 1. It is clearly shown that in shock phase of illness (day 4 to day 7), dengue virus disappeared rapidly

and dengue antibody rapidly increased at the same time. Thus, it is possible that during shock phase of THF there may be virus-antibody interaction to form circulating immune complex which may injure cells in the presence of a complement effector system.⁽¹⁴⁾ The studies of serum complement C3, a major component of complement system, revealed that C3 level was definitely decreased during the shock phase of illness in proportion to the severity of the disease^(15,16,17). Figure 2 illustrates the examples of serial C3 concentrations in the individual cases of each grade of THF. The reduction of C3 level occurred during day 4 to day 7 of disease (critical phase) in all grades. However, the shock cases (grade III and IV) had significantly

LOWEST VALUE OF C₃ LEVEL IN T.H.F.

DISEASE	No.	C ₃ mg % (mean ± S.D.)	p	
NORMAL	60	125.60 ± 26.57	-	
T.H.F.	GRADE I	21	92.26 ± 14.88	0.01
	GRADE II	96	71.51 ± 19.81	0.005
	GRADE III	28	54.10 ± 13.95	< 0.001
	GRADE IV	4	28.50 ± 25.99	< 0.001
	CONVALESCENT	34	150.44 ± 52.66	> 0.01
BACTERIAL INFECTION	18	133.87 ± 38.37	> 0.05	
VIRAL INFECTION	10	154.80 ± 38.09	> 0.01	

Table I Lowest value of C₃ levels in T.H.F. patients in each grade compares with C₃ level of 60 normal Thai children and children with bacterial and viral infections.

lower C₃ level than the non-shock cases (grade I and II). This can be clearly seen in Figure 3 when the lowest value of C₃ level from each patient in each grade are plotted and compared with the normal and convalescent C₃ values. The reduction of C₃ level in shock cases (grade III and grade IV) is statistically significant when compared to normal (Table I). However, there is no statistical difference of C₃ level between each grade. The reduction of C₃ level was not observed in other viral or bacterial infections⁽¹⁷⁾ (Table I). The marked reduction of complement C₃ during shock phase of THF may be due to activation of the complement system, although the decrease synthesis or the leakage of C₃ into extravascular space through the damage capillaries can not be ruled out⁽¹⁷⁾.

Thus, the observations of rapid disappearance of dengue virus from the blood and tissues of THF patients of a secondary dengue antibody (IgG) response in most cases of severe THF and of the marked reduction of complement during shock phase of illness in proportion to the severity of the disease, are consistent with the possible role of circulating immune complex in causing changes seen in the shock cases of THF⁽¹⁸⁾. Although the direct demonstration of circulating immune complex was still unsuccessful due to technical difficulty, a search for such immune complex is in progress. The activation of coagulation system as well as kallikrein-kinin system by immune complex are also under current investigations.

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