

The Determination of Complement Levels in Typhoid Fever

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OBJECTIVE: To determine the changes in complement levels in typhoid fever and their relationship to bacteremia and antibody response.

BACKGROUND: Information concerning alterations in the concentrations of complement components in infectious diseases are limited. Over the past several years this laboratory has demonstrated the involvement of complement in dengue shock syndrome, a viral illness which develops in situations of antibody excess with the formation of immune complexes. Complement activation is triggered by two known mechanisms. The classical pathway involving complement components C₁, C₄, and C₂ is activated by immune complexes, and the recently described alternate pathway involving C₃PA is triggered by endotoxin and immunocomplexes. Typhoid fever is caused by a gram negative bacillus, *Salmonella typhosa*. In cases of typhoid high levels of antibody are often reached in the continued presence of bacilli in the blood. Also *S. typhosa* is a gram negative organism and produces endotoxin. In typhoid fever, conditions for complement activation by both pathways are present. This study was designed to determine if a complement mediated immune mechanism is involved in the causation of typhoid fever and, if so, to determine the possible mechanisms of this activity.

METHODS: Patients: All patients admitted to Bangkok Children's Hospital with a clinical diagnosis of fever of unknown origin or enteric fever, whose duration of illness was longer than one week but not longer than 10 days, were admitted to the study.

Specimens: Each patient admitted to the study had blood taken for complete blood count, Widal serology, and determination of complement components on the day of admission and on the first, second, fourth, seventh, tenth and fourteenth day of hospitalization. Also, blood for bacterial culture was obtained on the day of admission and on the 1st, 2nd, and 4th day of hospitalization. Stools were collected for culture on the same days as the blood samples were drawn. Antibiotic therapy on patients diagnosed as having typhoid fever was commenced on the 3rd hospital day.

Bacteriological cultures: All isolations were performed in the clinical laboratory of the Bangkok Children's Hospital.

Serology: The Widal test was performed by the Bacteriology Department of this laboratory simultaneously on all specimens obtained from a single subject. A rise in the titer of both "O" and "H" antigens or high fixed titers (>1:160) of both were considered positive. Rises in either the "H" or "O" titers were considered equivocal and titers <1:160 with both antibodies were considered negative.

Complement Studies: Primary screening of complement level was done in the Virology Department of this laboratory using commercially prepared Radial Immunodiffusion tests for B_{1c}/B_{1a}. Aliquots of sera collected each day were frozen at -70C immediately upon separation of sera for determination of other complement components.

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Progress: At the time of writing, sampling and initial testing have been completed on 21 patients, aged 17 months to 13 years. Of these 21 patients, 15 had serological evidence of typhoid fever by the Widal test, one was equivocal, and five had negative antibody titers. Of the fifteen positive, eleven had high fixed titers. Five of these eleven had clear reductions in B_{1c}/B_{1a} levels on admission and/or on the 1st day of hospitalization. In all of these an increase in concentration was noted starting on the 4th to 7th day and approached the mean of the 5 typhoid negative febrile controls by the fourteenth day. There was no particular serological pattern associated with the reduction and rise in B_{1c}/B_{1a} level. A search for clinical correlation with the complement finding will be undertaken.

Serum samples from patients showing a marked drop in B_{1c}/B_{1a} levels will be further investigated. Concentrations of complement components $C1q$, $C4$, $C5$, C_3PA , and transferrin will be quantitated to confirm activation of complement and to determine which pathways of activation are involved.