CLINICAL CHARACTERISTICS, COMPLICATIONS AND TREATMENT OF SHIGELLOSIS

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INTRODUCTION.

Last year, preliminary investigation were presented on a striking complication of shigellosis, characterized by a micro angiopathic hemolytic anemia and occasionally by uremia. In the intervening year these studies have been expanded to explore factors triggering intravascular coagulation, complete the coagulation studies, collect histopathologic material and finally carefully characterize the clinical manifestations of uncomplicated shigellosis. A review of all shigellosis cases seen in Dacca hospital in 1975 has revealed many interesting vital statistics and emphasize the differences between the diseases of Shigella dysenteriae Type 1 and Shigella flexneri.

METHODS AND RESULTS.

A review of all shigellosis cases hospitalized in Dacca in 1975 (890 cases) has revealed several interesting vital statistics. S. dysenteriae accounts for one third of hospitalized and one-third of outpatient shigellosis visits, indicating that a higher percentage of this species do not require admission. Furthermore, the number of deaths in each group is in proportion to the number of admissions in each group. Children under age 5 account for most of the cases, but seem to account for an even greater proportion of the complications and deaths.

The children with leukemoid reaction account for only 5% of the total admissions. While the death rate among this group (primarily S. dysenteriae) is 20%, it accounts for only 12% of all shigella deaths. Thus, death due to

hemolysis, uremia, and toxic megacolon collectively account for a small portion of deaths in shigellosis. The most important causes of death is pneumonia, both gram negative pneumonia and aspiration pneumonia as a complication of intestinal ileus. Treatment of pneumonia in these patients presents a difficult problem and is currently under investigation.

It should be noted that about one-third of leukemoid cases occur in culture-negative cases. These cases need to be closely analyzed and pertussis and other known causes of leukemoid reaction must be indentified.

Since October 20, 120 patients with shigellosis have been studied prospectively according to protocol in our Shigellosis Research Unit in the Dacca hospital. Sixty per cent were S. dysenteriae Type 1 (Shiga bacillus) in children. An additional 8 cases of Sx. dysenteriae in adults are not discussed here. Compared with S. flexneri cases, children with S. dysenteriae infection with a more severe illness, despite reporting that the duration of illness prior to hospitalization was the same. Both the serum sodium and the serum specific gravity were markedly lower in the S. dysenteriae group. The hyponatremia probably is a sign of inappropriate ADH secretion, as well as underlying malnutrition. The hyposmolarity reflects proteinloss through the gut which is commonly greater than 10 gm lost per day, or 5-to 10-fold greater loss than that in cholera. When specific gravity falls below 1.018, mild to moderate pedal and generalized edema results (approx. 30% of our children).

Careful histories taken on admission reveal that 70% of children have been given prior medication, although most can not identify it by name. The first day of illness is typically characterized by watery diarrhea and fever, followed by mucous and bloody discharge with abdominal pain and tenesmus beginning on the second day. Rectal prolapse is very common and surprisingly is noticed with straining early in the course of the illness, by the third day, if it occurs. A fraction of these prolapses become consistently extended prolapses, seen only in S. dysenteriae and rarely in amoebiasis, never yet in S. flexneri. Degrees of malnutrition does not seem to be an important factors in

leading to prolapse, although as a common condition it exists in all our cases and makes clear analysis difficult.

Shigellosis patients form a large burden among all hospitalized cases. Their required hospitalization time is clearly longer, especially those with hemolysis, they require a more expensive drug, ampicillin, and they demand transfusion with fresh whole blood on an emergency basis, comprising over ¼ of all blood transfusions given in this hospital for the last 3 yrs. Thus hospitalized shigellosis cases form a burden on economic resources heretofore not discussed. Limited resources must be used wisely and policy decisions on outpatient and inpatient therapy should be made with the above information in mind.

The most important aspect in the clinical characterization of shigellosis is the description of the colities and proditis by proctoscopy and histology on biopsy specimens. We have performed 250 protoscopies and 80 rectal biopsies in the acute and convalescent stages of shigellosis. As the histopathologic work is just beginning, our experience with proctoscopy will not be described here.

The length of intestinal illness prior to the onset of leukemoid reaction and hemolysis might give a clue to the nature of the pathogenesis. The records of all leukemoid and hemolytic patients seen at this hospital since 1973 were reviewed. The accompanying table shows that the median and the mode of onset of the leukemoid reaction is on the 6th day of illness, and the median for the onset of significant hemolysis (hematocrit fall of 10 points) is on the 12th day of illness. Analysis of those patients studied since October with careful histories indicates the same medians, although these patients are few and the range of preceeding length of illness is broad. This data must be interpreted in the light of the difficulties of getting very accurate histories and also the fact that admission white counts greatly exceeding 50,000 may overestimate the preceding days of illness. Again the role of malnutrition is difficult to analyse in this syndrome, as the range of onsets and high prevalence of second and third degree malnutrition does not permit conclusions with our present data.

Several techniques have been employed to indentify the triggering factor in the hemolytic-uremic syndrome. All cases in 1975 with bacteremia were analyzed. The incidence of shigellemia is 5% in S. dysenteriae and 2% in S. flexneri. The striking incidence of gram negative bacteremia on admission, documented earlier for S. flexneri, is also present in S. dysenteriae cases. Clinical consequences associated with bacteremia included leukemoid reaction and hemolysis in only a small percentage. Since October 1975, 80 consecutive cases have had two admission blood cultures taken. None of the bacteremia cases developed hemolysis and none of hemolytic cases had bacteremia.

Thus other factors were sought. Serum, both acute + convalescent, has been collected for assay of circulating immune complexes by the Raji cell assay, to be performed at The University of New Mexico. Plasma was collected for assay of circulating endotoxin by the Linulus lysate technique performed by Dr. Jack Levin at Johns Hopkins. Preliminary results show a striking relationship between endotoxemia on admission and subsequent hemolysis.

If the circulating endotoxin is active pathogenetically, then complement should be fixed. Assays for serum complement components by the Mancini immunodiffusion technique revealed significant depressions of C3 component, while C4 and C3 proactivator components are less consistently depressed.

Coagulation studies are nearing completion. The thrombin time is prolonged in about 50% of the cases, whereas the Prothrombin time is rarely prolonged. The partial thromboplastin time was prolonged only in 4 severely ill cases who died. The most consistently depressed parameters were plasma fibrinogen and platelet count. These indicate that significant fibrin deposition is occurring despite the normalcy of the prothrombin time.

Red cell fragmentation remains the only consistent pathognomonic clinical sign. The Coombs antiglubulin test is negative and the enzyme glucose-6-phosphate dehydrogenase is present in red cells of hemolytic patients prior to hemolysis. Thus intrinsic red cell defects seem to be not involved.

A finding of great interest was the normal euglobulin lysis time. In most cases of D.I.C., the rate of activation of the fibrinolytic system is accelerated, thus shortening the systemic auglobulin lysis time.

It was observed in thrombotic thrombocytopenic purpura (TTP) that local fibrinolysis was retarded while systemic fibrinolysis was normal. The coagulation picture in our cases parallells very closely that found in TTP, as well as idopathic hemolytic-uremic syndrome. Thus it seems that the degree of fibrin-deposition occurring may be dependent on the length of endotoxin exposure, and the degree to which thrombotic complications appear is dependent on the activity of the local fibrinolytic system.

If the former is true, then more rapid clearance of the shigella organism, and hence endotoxin, may be achieved by superior antimicrobial therapy. This indeed has been shown here. The average dose of ampicillin of 50-80 mg/kg given routinely to patients in January through May of 1975 was compared to those shigellosis cases admitted since November 1975 receiving ampicillin 100 mg/kg. At P value of 1% the higher dose level had significantly less cases of hemolysis, despite the same number of cases with leukemoid reaction on admission. Thus the first line of defense against hemolysis is rapid treatment of the invading shigella. It is unlikely that treatment itself precipitates hemolysis.

Further efforts will be directed at defining the nature of the microangipathy itself. Scanning electron microscopy of cross-sections of rectal mucosa is anticipated, as well as indirect assays of local fibrinolysis in the rectal mucosal vesculature, and immunofluorescent studies of antigen localization in the rectal mucosa.

Finally, an interesting observation has been made concerning persistent colitis in infants suffering from acute dysentery due to S. dysenteriae. Only 4 cases have been identified (incidence of 5 per cent) by the following criteria: inability to culture to the shigella organism from stool or biopsy; persisting leukocytosis without fe

continuing liquid mucoid diarrhea; fecal leukocyte excretion parallelled by the proctoscopic appearance of friability and inflammation and cobblestoning of the rectal mucosa. Without histopathological material (in preparation) further conclusions on the nature of this persistent colitis are not possible.