The Importance of Nonrenal Involvement in Hemolytic-Uremic Syndrome

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ABSTRACT. Fifteen children with the clinical manifestations of hemolytic-uremic syndrome are reported. Prompt recognition of the syndrome and effective therapy for acute renal failure including early dialysis were instituted in each case. Analysis of the clinical course and histopathologic features in these patients indicated that early dialysis and effective management of acute renal failure may unmask evidence of nonrenal involvement; microthrombi may be found in a wide distribution of organs, including the brain and myocardium; and extent and severity of nonrenal involvement become an important determinant of ultimate prognosis. Pediatrics 65: 115-120, 1980; hemolytic-uremic syndrome, microangiopathy, microthrombi.

In 1955, Gasser and associates first reported patients with the hemolytic-uremic syndrome (HUS). Currently, three clinical features—microangiopathic hemolytic anemia, thrombocytopenia, and azotemia—are used to define the syndrome. Early reports include mostly young children and a high mortality. More recently, patients of all ages with HUS, including adults, have been reported. With early recognition of the syndrome and improved technology for the treatment of acute renal failure, mortality has declined but remains at between 10% and 20%. Although multiple factors may contribute to this residual death rate, this report will focus attention on the importance of nonrenal involvement in HUS.

Over the past several years, the belief has evolved that HUS is a pathophysiologic state in which intravascular coagulation is localized in the renal vasculature and limited to the kidney. The purpose of this report is to emphasize the microangiopathic involvement of a number of organ systems in HUS and to suggest that the cause of the residual mortality in this disease may be related to the severity of nonrenal involvement.

METHODS AND MATERIALS

Patient Population

All children with the clinical features of HUS who were admitted to Yale-New Haven Hospital or St. Raphael's Hospital between 1971 and 1977 form the basis of this report. All 15 children had microangiopathic hemolytic anemia, thrombocytopenia, and azotemia. The degree of renal involvement was assessed on a daily basis, and appropriate clinical management of reduced renal function was initiated promptly. Once substantial renal involvement had been documented, hemodialysis or peritoneal dialysis was initiated early in the course of treatment using standard techniques. Elevations in blood pressure were controlled with standard medications. None of the patients was treated with steroids, anticoagulants, or immunosuppressive agents.

Histopathologic Materials

All sections from the autopsy materials from the three patients who died were reviewed. At the time of autopsy, all tissues were fixed in 10% neutral formalin. Paraffin-embedded sections were stained with hematoxylin and eosin. Special emphasis was placed on the presence and distribution of thrombi and any associated tissue changes. Two histologic patterns of thrombi were present: a loose fibrin meshwork with entrapped leukocytes and red blood cells (Figs 1 and 2) and a coarse granular aggrega-
tion of eosinophilic material that was often acellular (Figs 2 to 4). Some thrombi were biphasic, exhibiting each pattern immediately juxtaposed (Fig 5). These thrombi were present in arterioles and capillary-postcapillary venular complexes. These lesions were at least 24 hours old but less than seven days old.

In two cases, sections of kidney tissue were stained with Putt's fibrin stain, and tissue was treated with fluorescein isothiocyanate-labeled antisera for immunofluorescent microscopy.

In all cases, complete autopsy findings were carefully reviewed. In each case, observations other than microthrombus formation were nonspecific and simply corroborated the clinical events.
Fig 5. In thymus, biphasic thrombus with granular portion (curved black arrow) and fibrin strand portion (white arrow) in postcapillary venule. Second thrombus can be seen in upper left corner of the field (hematoxylin-eosin, original magnification x250).

Fig 6. Thin-walled arteriole with dilated Virchow-Robin space in basal ganglia of brain. Lumen contains fibrin strand thrombus (arrow) and entrapped leukocytes (hematoxylin-eosin, original magnification x250).

RESULTS

The clinical characteristics of all 15 patients are given in Table 1. The patient’s ages at the onset of disease ranged from 6 weeks to 22 years. Ten of the 15 patients had oliguria (output of less than 15 ml/kg/day of urine) that lasted from three to 108 days. Eight patients required dialysis, and dialysis was first performed on seven of these eight within five days of presentation. Only one patient (No. 8) had more than one day of oliguria without dialysis because a mild diuresis ensued on the sixth day. Neurologic symptoms, which included predominantly focal or generalized seizures, stupor, or coma, were seen in five patients. On the basis of the outcome of the cases, three groups were differentiated. All clinically apparent abnormalities in each group are reported.

The recovery group consists of ten patients. Four of these patients developed oliguria, which persisted for 1 to 15 days, and three of these four patients required at least one dialysis. Transient hypertension was seen in only one patient (No. 10) and was easily controlled. Focal seizures were encountered in two of these patients when neither patient was uremic or hypertensive. These seizures were easily controlled with conventional doses of phenobarbital. All ten patients recovered renal function completely and have had no clinical sequelae six months to six years after their acute HUS.

The morbidity group consists of two patients. Both patients had prolonged oliguria and required maintenance dialysis. Their clinical courses were similar in that severe refractory hypertension developed in both patients, and both required bilateral nephrectomy for control of hypertension. Neither patient developed neurologic symptoms despite severe hypertension and uremia. In addition, there was no clinical evidence of nonrenal involvement during the course of their illness or during the follow-up period. Both children have received a renal homograft and are clinically well five and seven years after the onset of the disease.

The mortality group consists of three patients, all of whom died within eight days of admission. All three patients were oliguric throughout their hosp-
hospital course and required frequent dialysis, which was initiated within three days of admission in each case. Severe neurologic symptoms were present in all three cases. These included stupor, hallucinations, disorientation, seizures, and coma. One patient (No. 14) was comatose throughout her clinical course despite rigorous dialysis and supportive care. In another patient (No. 13), seizures persisted despite maximal anticonvulsant therapy including an intravenous xylocaine infusion. In addition, patient No. 15 had clinical evidence of myocardial ischemia manifested by a persistent tachycardia, ST-T wave changes on ECG, and an elevated SGOT level. At the time of admission, these patients were more ill than the other 12 children; despite maximal supportive therapy including early dialysis, all three died. Two patients (No. 13 and No. 14) had a cerebral death with cessation of brain function; the other patient (No. 15) died of refractory hypotension.

An evaluation of the extent and severity of microangiopathic involvement in the three patients who died was of particular interest. The distribution of microthrombi in various organs is given in Table 2. Eight organs (kidney, lung, heart, liver, adrenal glands, brain, thyroid, and pancreas) were examined in all three cases (Figs 1 to 7). Microthrombi were present in two organs (kidney and lung) in each case, in four organs (heart, liver, adrenal gland, and brain) in two of the three cases, and in two organs (thyroid and pancreas) in one of the three cases. Thymus, lymph nodes, and colon were examined in only two cases, and microthrombi were documented in each case in which these three organs were examined. Microthrombi were also found in the bladder, esophagus, and ovary in the one patient in whom these tissues were examined.

Evidence of ischemia also was present in most organ systems examined, especially the brain. All three cases (including the case without microthrombi) had histologic evidence of brain involvement. Focal areas of infarction with surrounding edema and necrosis were seen in the cerebral cortex of each patient (Figs 1, 6, and 7). In one patient, similar areas were found in the basal ganglion. In two cases, there were focal areas of necrosis within the myocardium. Interestingly, a severe ischemic enterocolitis was seen in two patients, both of whom had bloody diarrhea.

In all three cases, the renal findings were typical of HUS. Two cases had bilateral cortical necrosis, and all three had abundant eosinophilic thrombi in glomerular capillary lumina and in arterioles. Putt’s fibrin stain indicated that the glomerular thrombi contained fibrin. Immunofluorescent staining showed a granular pattern along the glomerular basement membrane for fibrin.
DISCUSSION

Over the past decade, HUS has become a well-recognized and clearly defined clinical entity. It also has become clear that the salient features of this syndrome—azoemia, thrombocytopenia, and microangiopathic hemolytic anemia—may occur in a number of clinical settings and, thus, HUS represents a syndrome and not a specific disease. In children, HUS is usually idiopathic in origin and preceded by a gastrointestinal or upper respiratory prodrome. The importance of specific prodromal features, clinical manifestations, therapeutic considerations, and prognosis has been reviewed.

The earliest reports of HUS concentrated on its occurrence in infants and young children and reported a high mortality (50% to 80%). Since those early reports, the prognosis has improved considerably and the residual mortality has declined to between 10% and 20%. It seems likely that several factors have contributed to this improvement in ultimate prognosis: early recognition and diagnosis of HUS; reporting of milder cases; prompt and appropriate management of acute renal failure; improved technology for the support of infants and children with renal failure; and early dialysis of the most severely affected children. Kaplan and associates have shown that prompt recognition of the syndrome and early institution of dialysis contributed to a decline in mortality from 77% to 10% in severely affected patients. Likewise, Schwartz and Barratt have presented evidence that the duration of symptoms before dialysis is an important prognostic factor. In their study of 25 children, those patients on whom dialysis was performed within 20 days of onset of symptoms had markedly improved recovery. In the present series of patients, all of the factors believed to favorably influence prognosis were established. In each case, the syndrome was recognized early, and prompt and appropriate management of acute renal failure was instituted. Once the severity of renal involvement had been established, dialysis was instituted after 48 hours of oliguria or within eight days of onset of disease in all patients except one (No. 8), who was oliguric for five days and had a mild diuresis starting just before institution of dialysis. Most importantly, dialysis had been started within 72 hours of admission in all three patients who died. Thus, a detailed analysis of the three patients who died may provide important information about factors that contribute to the residual mortality in HUS.

The most striking features of the three children who died were the severity of clinical presentation manifested by multisystem involvement from onset of disease, and the extent and distribution of microangiopathy at postmortem examination. The degree of neurologic involvement in the three patients who died was considerably more severe than that observed in the two children with neurologic symptoms who recovered. One of the children who died was comatose through the clinical course, and another child had uncontrollable seizures. Although central nervous system involvement occurs in between 30% to 50% of reported cases, the severity and extent of neurologic findings is usually considerably less than that observed in these three cases, and major neurologic symptoms are considered a poor prognostic sign.

In addition to neurologic symptoms, there was evidence of myocardial involvement in one of the patients who died (No. 15). In most series, myocardial involvement has been attributed to the metabolic consequences of acute renal failure, such as hyperkalemia, hypocalcemia, volume overload, hypertension, or anemia. Gianantonio et al have reported five children with findings of myocardial injury that could not be accounted for by uremia or volume factors. In addition, Lieberman has documented one case of myocarditis. In the present series, the myocardial insult in patient No. 15 was not related to uremia or metabolic factors.

Severe pulmonary insufficiency that required mechanical respiration for ventilation and oxygenation developed in all three patients who died. This problem was not related to volume overload, pulmonary edema, or congestive heart failure, and did not respond to dialysis.

In the present series of patients, the severity of renal involvement based on maximum serum creatinine values and duration of oliguria was similar in the morbidity and mortality groups of patients. The major clinical difference between these groups was in the extent and severity of nonrenal involvement. There was no clinical evidence in either of the children in the morbidity group of multiple organ-system involvement either during their acute illness or during an extended period of follow-up (five and seven years).

Another striking and somewhat intriguing finding was the distribution of microangiopathy in the three patients who died. Microthrombi and severe ischemic changes were found in a wide spectrum of organ systems (Figs 1–7). In previous reports, some investigations have demonstrated microthrombi in multiple organs, whereas others have maintained that intravascular coagulation was limited to the kidney. In fact, based on some of these reports and coagulation studies, some have suggested that HUS represents a pathophysiologic state in which intravascular coagulation is limited to the renal vasculature. Several factors may contribute to these apparent discrepancies. Diffuse microthrombi are reported in early studies that described the
pathologic findings in the most severely affected patients who had, for the most part, died early in the course of disease. Microangiopathy limited to the kidney is found in later reports in which many patients died two months or more after onset, and the cause of death was frequently related to complications of dialysis therapy. The relationship of the duration of disease before autopsy to the distribution of microangiopathy is illustrated by the findings of Gianantonio and associates. This group studied autopsy materials from 47 cases of HUS. Thrombosis in small vessels was found outside the kidneys in 20 of 26 patients who died during the first two weeks of illness. The distribution of organs involved was similar to that reported in the present study, including small vessel thrombosis in the brain and myocardium. Of 21 autopsies from patients who died more than one month after onset, no extrarenal vascular thrombi were noted. In the present report, all three patients died within eight days of admission. In view of the clinical manifestations, it is not surprising that widespread microangiopathy might be present. In addition, previous studies have not been limited to patients who received early and aggressive supportive care. Thus, it is possible that some autopsy studies include patients in whom disease was limited to the kidneys, but the patients died because of complications of acute renal failure. In such cases, it is possible that diffuse microthrombi were not present. Although extensive tissues from the patients in the recovery and morbidity group of the present study were not available for histopathologic analysis, it seems unlikely that extensive microthrombi would be present based on the lack of clinical manifestations during the acute illness and recovery period (six months to six years).

At present, one cannot determine whether the more severe cases are really another disease instead of a part of the spectrum of HUS. Prominent CNS involvement and diffuse microthrombus formation are consistent with thrombotil thrombocytopenia purpura. Considering the overlapping clinical features of these diseases and the lack of an established etiology for either disorder, any attempt to definitively discriminate between these syndromes becomes hazardous and largely semantic.

A careful analysis of the clinical course and histopathologic findings in the present series of patients provides several important observations. Early and aggressive management of renal failure may result in the survival of patients with mild HUS in whom extrarenal manifestations are neither severe nor extensive, and of patients in whom severe involvement is limited to the kidneys. In patients with more extensive and diffuse disease, effective treatment of acute renal failure may allow the extent and severity of nonrenal involvement to become more clinically evident than previously appreciated. The appearance of nonrenal manifestations does not, however, preclude a successful outcome. Microangiopathy with microthrombus formation may be seen in a number of organs in children with diffuse disease who die early in the course of the illness. The extent of nonrenal involvement has become an important factor in HUS and may account, in part, for the residual morbidity and mortality in this disease.

REFERENCES

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Pediatrics 1980;65;115

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The Importance of Nonrenal Involvement in Hemolytic-Uremic Syndrome
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*Pediatrics* 1980;65;115

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